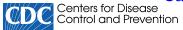
EXHIBIT 232



Vaccines & Immunizations

Glossary

A

Acellular vaccine: Listen ([MP3]

A vaccine containing partial cellular material as opposed to complete cells.

Acquired Immune Deficiency Syndrome (AIDS): A medical condition where the immune system cannot function properly and protect the body from disease. As a result, the body cannot defend itself against infections (like pneumonia). AIDS is caused by the Human Immunodeficiency Virus (HIV). This virus is spread through direct contact with the blood and body fluids of an infected individual. High risk activities include unprotected sexual intercourse and intravenous drug use (sharing needles). There is no cure for AIDS, however, research efforts are on-going to develop a vaccine.

Active immunity: The production of antibodies against a specific disease by the immune system. Active immunity can be acquired in two ways, either by contracting the disease or through vaccination. Active immunity is usually permanent, meaning an individual is protected from the disease for the duration of their lives.

A short-term, intense health effect.

Adjuvant: Listen ([MP3]

A substance (e.g. aluminum salt) that is added during production to increase the body's immune response to a vaccine.

Adverse events: Undesirable experiences occurring after immunization that may or may not be related to the vaccine.

Advisory Committee on Immunization Practices (ACIP): A panel of 10 experts who make recommendations on the use of vaccines in the United States. The panel is advised on current issues by representatives from the Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health, American Academy of Pediatrics, American Academy of Family Physicians, American Medical Association and others. The recommendations of the ACIP guide immunization practice at the federal, state and local level.

Allergy: A condition in which the body has an exaggerated response to a substance (e.g. food or drug). Also known as hypersensitivity.

Anaphylaxis: Listen ([MP3]

An immediate and severe allergic reaction to a substance (e.g. food or drugs). Symptoms of anaphylaxis include breathing difficulties, loss of consciousness and a drop in blood pressure. This condition can be fatal and requires immediate medical attention.

Anthrax: Listen **()** [MP3]

An acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax most commonly occurs in hoofed mammals and can also infect humans.

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Antibiotic: Listen **◎** [MP3] A substance that fights bacteria.

Antibody: Listen ([MP3]

A protein found in the blood that is produced in response to foreign substances (e.g. bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.

Antigens: Listen ([MP3]

Foreign substances (e.g. bacteria or viruses) in the body that are capable of causing disease. The presence of antigens in the body triggers an immune response, usually the production of antibodies.

Antitoxin: Listen ([MP3]

Antibodies capable of destroying toxins generated by microorganisms including viruses and bacteria.

Antiviral: Literally "against-virus" — any medicine capable of destroying or weakening a virus.

Arthralgia: Listen (IMP3)

Joint pain.

Arthritis: A medical condition characterized by inflammation of the joints which results in pain and difficulty moving.

Association: The degree to which the occurrence of two variables or events is linked. Association describes a situation where the likelihood of one event occurring depends on the presence of another event or variable. However, an association between two variables does not necessarily imply a cause and effect relationship. The term association and relationship are often used interchangeably. See causal and temporal association.

Asthma: A chronic medical condition where the bronchial tubes (in the lungs) become easily irritated. This leads to constriction of the airways resulting in wheezing, coughing, difficulty breathing and production of thick mucus. The cause of asthma is not yet known but environmental triggers, drugs, food allergies, exercise, infection and stress have all been implicated.

Asymptomatic infection: Listen ([MP3]

The presence of an infection without symptoms. Also known as inapparent or subclinical infection.

Attenuated vaccine: Listen ([MP3]

A vaccine in which live virus is weakened (attenuated) through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines currently licensed in the United States include measles, mumps, rubella, varicella, rotavirus, yellow fever, smallpox, and some formulations of influenza, shingles, and typhoid vaccines. Also known as a *live vaccine*.

Autism: A chronic developmental disorder usually diagnosed between 18 and 30 months of age. Symptoms include problems with social interaction and communication as well as repetitive interests and activities. At this time, the cause of autism is not known although many experts believe it to be a genetically based disorder that occurs before birth.

В

B cells: Small white blood cells that help the body defend itself against infection. These cells are produced in bone marrow and develop into plasma cells which produce antibodies. Also known as B lymphocytes.

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Bacteria: Tiny one-celled organisms present throughout the environment that require a microscope to be seen. While not all bacteria are harmful, some cause disease. Examples of bacterial disease include diphtheria, pertussis, tetanus, *Haemophilus influenzae*, and pneumococcal.

Bias: Flaws in the collection, analysis or interpretation of research data that lead to incorrect conclusions.

Biological plausibility: A causal association (or relationship between two factors) is consistent with existing medical knowledge.

Bone marrow: Soft tissue located within bones that produce all blood cells, including the ones that fight infection.

Booster shots: Additional doses of a vaccine needed periodically to "boost" the immune system. For example, the tetanus and diphtheria (Td) vaccine which is recommended for adults every ten years.

Brachial neuritis: Listen ([MP3]

Inflammation of nerves in the arm causing muscle weakness and pain.

Breakthrough infection: Development of a disease despite a person's having responded to a vaccine.

\mathbf{C}

Causal association: Listen ([MP3]

The presence or absence of a variable (e.g. smoking) is responsible for an increase or decrease in another variable (e.g. cancer). A change in exposure leads to a change in the outcome of interest.

Chickenpox: See Varicella.

Chronic health condition: A health related state that lasts for a long period of time (e.g. cancer, asthma).

Combination vaccine: Two or more vaccines administered in a single dose in order to reduce the number of shots given. For example, the MMR (measles, mumps, rubella) vaccine.

Communicable: That which can be transmitted from one person or animal to another. Also known as infectious.

Crohn's disease: Listen ([MP3]

A chronic medical condition characterized by inflammation of the bowel. Symptoms include abdominal pain, diarrhea, fever, loss of appetite and weight loss. The cause of Crohn's disease is not yet known, but genetic, dietary and infectious factors may play a part.

Community immunity: A situation in which a sufficient proportion of a population is immune to an infectious disease (through vaccination and/or prior illness) to make its spread from person to person unlikely. Even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the community. Also known as herd immunity.

Conjugate vaccine: Listen ([MP3]

The joining together of two compounds (usually a protein and polysaccharide) to increase a vaccine's effectiveness.

Conjunctivitis: Listen © [MP3] 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 5 of 497

Inflammation of the mucous membranes surrounding the eye causing the area to become red and irritated. The membranes may be irritated because of exposure to heat, cold or chemicals. This condition is also caused by viruses, bacteria or allergies.

Contraindication: Listen ([MP3]

A condition in a recipient which is likely to result in a life-threatening problem if a vaccine were given.

Convulsion: See Seizure.

Crib or Cot Death: See Sudden Infant Death Syndrome (SIDS).

D

Deltoid: Listen **()** [MP3]

A muscle in the upper arm where shots are usually given.

Demyelinating disorders: Listen **()** [MP3]

A medical condition where the myelin sheath is damaged. The myelin sheath surrounds nerves and is responsible for the transmission of impulses to the brain. Damage to the myelin sheath results in muscle weakness, poor coordination and possible paralysis. Examples of demyelinating disorders include Multiple Sclerosis (MS), optic neuritis, transverse neuritis and Guillain-Barre Syndrome (GBS).

Diabetes: A chronic health condition where the body is unable to produce insulin and properly breakdown sugar (glucose) in the blood. Symptoms include hunger, thirst, excessive urination, dehydration and weight loss. The treatment of diabetes requires daily insulin injections, proper nutrition and regular exercise. Complications can include heart disease, stroke, neuropathy, poor circulation leading to loss of limbs, hearing impairment, vision problems and death.

Diphtheria: Listen (MP3)

A bacterial disease marked by the formation of a false membrane, especially in the throat, which can cause death.

Disease: Sickness, illness or loss of health.

E

Efficacy rate: Listen (MP3)

A measure used to describe how good a vaccine is at preventing disease.

Encephalitis: Listen ([MP3]

Inflammation of the brain caused by a virus. Encephalitis can result in permanent brain damage or death.

Encephalopathy: Listen (MP3)

A general term describing brain dysfunction. Examples include encephalitis, meningitis, seizures and head trauma.

Epidemic: Listen (MP3)

The occurrence of disease within a specific geographical area or population that is in excess of what is normally expected.

Endemic: Listen (MP3)

The continual, low-level presence of disease in a community

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Erythema Multiforme: Listen (MP3)

A medical condition characterized by inflammation of the skin or mucous membranes (including the mouth, throat and eyes). Erthema Multiforme has been reported following infection. Symptoms persist anywhere from 2 days to 4 weeks and include skin lesions, blisters, itching, fatigue, joint pain and fever.

Etiology: Listen (MP3)

The cause of.

Exposure: Contact with infectious agents (bacteria or viruses) in a manner that promotes transmission and increases the likelihood of disease.

F

Febrile: Listen **()** [MP3] Relating to fever; feverish.

G

Guillain-Barre Syndrome (GBS): Listen © [MP3]

A rare neurological disease characterized by loss of reflexes and temporary paralysis. Symptoms include weakness, numbness, tingling and increased sensitivity that spreads over the body. Muscle paralysis starts in the feet and legs and moves upwards to the arms and hands. Sometimes paralysis can result in the respiratory muscles causing breathing difficulties. Symptoms usually appear over the course of one day and may continue to progress for 3 or 4 days up to 3 or 4 weeks. Recovery begins within 2-4 weeks after the progression stops. While most patients recover, approximately 15%-20% experience persistent symptoms. GBS is fatal in 5% of cases.

Η

Haemophilus influenzae type b (Hib): Listen ◎ [MP3]

A bacterial infection that may result in severe respiratory infections, including pneumonia, and other diseases such as meningitis.

Hepatitis A: A minor viral disease, that usually does not persist in the blood; transmitted through ingestion of contaminated food or water.

Hepatitis B: A viral disease transmitted by infected blood or blood products, or through unprotected sex with someone who is infected.

Hepatitis C: is a liver disease caused by the Hepatitis C virus (HCV), which is found in the blood of persons who have the disease. HCV is spread by contact with the blood of an infected person.

Hepatitis D: is a defective virus that needs the hepatitis B virus to exist. Hepatitis D virus (HDV) is found in the blood of persons infected with the virus.

Hepatitis E: is a virus (HEV) transmitted in much the same way as hepatitis A virus. Hepatitis E, however, does not often occur in the United States.

Herd immunity: See Community immunity.

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Herpes Zoster: A disease characterized by painful skin lesions that occur mainly on the trunk (back and stomach) of the body but which can also develop on the face and in the mouth. Complications include headache, vomiting, fever and meningitis. Recovery may take up to 5 weeks. Herpes Zoster is caused by the same virus that is responsible for chickenpox. Most people are exposed to this virus during childhood. After the primary infection (chickenpox), the virus becomes dormant, or inactivated. In some people the virus reactivates years, or even decades, later and causes herpes zoster. Also known as the shingles.

Hives: The eruption of red marks on the skin that are usually accompanied by itching. This condition can be caused by an allergy (e.g. to food or drugs), stress, infection or physical agents (e.g. heat or cold). Also known as uticaria.

Hypersensitivity: Listen **()** [MP3]

A condition in which the body has an exaggerated response to a substance (e.g. food or drug). Also known as an allergy.

Hyposensitivity: Listen **()** [MP3]

A condition in which the body has a weakened or delayed reaction to a substance.

T

A protein found in the blood that fights infection. Also known as gamma globulin.

Immune system: The complex system in the body responsible for fighting disease. Its primary function is to identify foreign substances in the body (bacteria, viruses, fungi or parasites) and develop a defense against them. This defense is known as the immune response. It involves production of protein molecules called antibodies to eliminate foreign organisms that invade the body.

Immunity: Protection against a disease. There are two types of immunity, passive and active. Immunity is indicated by the presence of antibodies in the blood and can usually be determined with a laboratory test. See active and passive immunity.

Immunization: Listen ([MP3]

The process by which a person or animal becomes protected against a disease. This term is often used interchangeably with vaccination or inoculation.

Immunosupression: Listen ([MP3]

When the immune system is unable to protect the body from disease. This condition can be caused by disease (like HIV infection or cancer) or by certain drugs (like those used in chemotherapy). Individuals whose immune systems are compromised should not receive live, attenuated vaccines.

Inactivated vaccine: Listen ([MP3]

A vaccine made from viruses and bacteria that have been killed through physical or chemical processes. These killed organisms cannot cause disease.

Inapparent infection: The presence of infection without symptoms. Also known as subclinical or asymptomatic infection.

Incidence: The number of new disease cases reported in a population over a certain period of time.

Incubation period: The time from contact with infectious agents (bacteria or viruses) to onset of disease.

Exhibit 232

Infectious: Capable of spreading disease. Also known as communicable.

Infectious agents: Organisms capable of spreading disease (e.g. bacteria or viruses).

Inflammation: Redness, swelling, heat and pain resulting from injury to tissue (parts of the body underneath the skin). Also known as swelling.

Inflammatory Bowel Disease (IBD): A general term for any disease characterized by inflammation of the bowel. Examples include colitis and Crohn's disease. Symptoms include abdominal pain, diarrhea, fever, loss of appetite and weight loss.

Influenza: A highly contagious viral infection characterized by sudden onset of fever, severe aches and pains, and inflammation of the mucous membrane.

A type of bowel blockage that happens when one portion of the bowel slides into the next, much like the pieces of a telescope; it is treated in a hospital and may require surgery.

Investigational vaccine: A vaccine that has been approved by the Food and Drug Administration (FDA) for use in clinical trials on humans. However, investigational vaccines are still in the testing and evaluation phase and are not licensed for use in the general public.

J

Jaundice: Listen ([MP3]

Yellowing of the skin and eyes. This condition is often a symptom of hepatitis infection.

Ţ,

Lesion: Listen (MP3)

An abnormal change in the structure of an organ, due to injury or disease.

Live vaccine: A vaccine in which live virus is weakened (attenuated) through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Live vaccines currently licensed in the United States include measles, mumps, rubella, varicella, rotavirus, yellow fever, smallpox, and some formulations of influenza, shingles, and typhoid vaccines. Also known as an *attenuated vaccine*.

Lupus: A disease characterized by inflammation of the connective tissue (which supports and connects all parts of the body). Chronic swelling of the connective tissue causes damage to the skin, joints, kidneys, nervous system and mucous membranes. The disease begins with fever, joint pain and fatigue. Additional symptoms continue to develop over the years including nausea, fatigue, weight loss, arthritis, headaches and epilepsy. Problems with heart, lung and kidney function may also result. This condition is diagnosed most frequently in young women but also occurs in children.

Lymphocytes: Listen ([MP3]

Small white blood cells that help the body defend itself against infection. These cells are produced in bone marrow and develop into plasma cells which produce antibodies. Also known as B cells.

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Macrophage: Listen ([MP3]

A large cell that helps the body defend itself against disease by surrounding and destroying foreign organisms (viruses or bacteria).

Macular: Listen ([MP3]

Skin lesions, normally red-colored.

Measles: A contagious viral disease marked by the eruption of red circular spots on the skin.

Memory Cell: A group of cells that help the body defend itself against disease by remembering prior exposure to specific organisms (e.g. viruses or bacteria). Therefore these cells are able to respond quickly when these organisms repeatedly threaten the body.

Meningitis: Listen (MP3)

Inflammation of the brain and spinal cord that can result in permanent brain damage and death.

Meningoencephalitis: Listen (MP3)

["men in joe en sef uh LIGHT iss"] — inflammation of the brain and meninges (membranes) that involves the encephalon (area inside the skull) and spinal column.

Microbes: Listen ([MP3]

Tiny organisms (including viruses and bacteria) that can only be seen with a microscope.

The soft, wet tissue that lines body openings specifically the mouth, nose, rectum and vagina.

Multiple Sclerosis: Listen ([MP3]

Multiple sclerosis (MS) is a disease of the central nervous system characterized by the destruction of the myelin sheath surrounding neurons, resulting in the formation of "plaques." MS is a progressive and usually fluctuating disease with exacerbations (patients feeling worse) and remissions (patients feeling better) over many decades. Eventually, in most patients, remissions do not reach baseline levels and permanent disability and sometimes death occurs. The cause of MS is unknown. The most widely held hypothesis is that MS occurs in patients with a genetic susceptibility and that some environmental factors "trigger" exacerbations. MS is 3 times more common in women than men, with diagnosis usually made as young adults. Also see demyelinating disorders.

Mumps: Acute contagious viral illness marked by swelling, especially of the parotid glands.

N

Neuritis: Listen **()** [MP3] Inflammation of the nerves.

Neuropathy: Listen ([MP3]

A general term for any dysfunction in the peripheral nervous system. Symptoms include pain, muscle weakness, numbness, loss of coordination and paralysis. This condition may result in permanent disability.

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Optic neuritis: Listen ([MP3]

A medical condition where vision deteriorates rapidly over hours or days. One or both eyes may be affected. This condition results for the demyelination of optic nerves. In most cases, the cause of optic neuritis is unknown. Patients may regain their vision or be left with permanent impairment. Also see demyelinating disorders.

Orchitis: Listen ([MP3]

A complication of mumps infection occurring in males (who are beyond puberty). Symptoms begin 7-10 days after onset of mumps and include inflammation of the testicles, headache, nausea, vomiting, pain and fever. Most patients recover but in rare cases sterility occurs.

Otitis Media: Listen (MP3)

A viral or bacterial infection that leads to inflammation of the middle ear. This condition usually occurs along with an upper respiratory infection. Symptoms include earache, high fever, nausea, vomiting and diarrhea. In addition, hearing loss, facial paralysis and meningitis may result.

Outbreak: Sudden appearance of a disease in a specific geographic area (e.g. neighborhood or community) or population (e.g., adolescents).

P

Pandemic: An epidemic occurring over a very large geographic area.

Papular: Listen (MP3)

Marked by small red-colored elevation of the skin.

Passive immunity: Protection against disease through antibodies produced by another human being or animal. Passive immunity is effective, but protection is generally limited and diminishes over time (usually a few weeks or months). For example, maternal antibodies are passed to the infant prior to birth. These antibodies temporarily protect the baby for the first 4-6 months of life.

Pathogens: Organisms (e.g. bacteria, viruses, parasites and fungi) that cause disease in human beings.

(whooping cough) Bacterial infectious disease marked by a convulsive spasmodic cough, sometimes followed by a crowing intake of breath.

Petechiae: Listen ([MP3]

["pe TEEK ee ay"] — a tiny reddish or purplish spot on the skin or mucous membrane, commonly part of infectious diseases such as typhoid fever.

Placebo: A substance or treatment that has no effect on human beings.

Pneumonia: Listen ([MP3]

Inflammation of the lungs characterized by fever, chills, muscle stiffness, chest pain, cough, shortness of breath, rapid heart rate and difficulty breathing.

Poliomyelitis: Listen ([MP3]

(polio) An acute infectious viral disease characterized by fever, paralysis, and atrophy of skeletal muscles.

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Polysaccharide vaccines: Listen ([MP3]

Vaccines that are composed of long chains of sugar molecules that resemble the surface of certain types of bacteria. Polysaccharide vaccines are available for pneumococcal disease, meningococcal disease and *Haemophilus Influenzae* type b.

Potency: A measure of strength.

Precaution: A condition in a recipient which may result in a life-threatening problem if the vaccine is given, or a condition which could compromise the ability of the vaccine to produce immunity.

Prevalence: The number of disease cases (new and existing) within a population over a given time period.

Prodromal: Listen ([MP3]

An early symptom indicating the onset of an attack or a disease.

Q

Quarantine: The isolation of a person or animal who has a disease (or is suspected of having a disease) in order to prevent further spread of the disease.

R

Of or resulting from new combinations of genetic material or cells; the genetic material produced when segments of DNA from different sources are joined to produce recombinant DNA.

Reye Syndrome: Listen ([MP3]

Encephalopathy (general brain disorder) in children following an acute illness such as influenza or chickenpox. Symptoms include vomiting, agitation and lethargy. This condition may result in coma or death.

Residual Seizure Disorder (RSD): See seizures.

Risk: The likelihood that an individual will experience a certain event.

Rotavirus: Listen (MP3)

A group of viruses that cause diarrhea in children.

Rubella: (German measles) Viral infection that is milder than normal measles but as damaging to the fetus when it occurs early in pregnancy.

Rubeola: Listen (MP3]

See Measles.

S

Seroconversion: Listen ([MP3]

Development of antibodies in the blood of an individual who previously did not have detectable antibodies.

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Serology: Listen ([MP3]

Measurement of antibodies, and other immunological properties, in the blood serum.

Serosurvey: Listen ([MP3]

Study measuring a person's risk of developing a particular disease.

Seizure: The sudden onset of a jerking or staring spell. Many seizures following a vaccination are caused by fever. Seizures are also known as convulsions.

Severe Combined immune Deficiency (SCID): Included in a group of rare, life-threatening disorders caused by at least 15 different single gene defects that result in profound deficiencies in T- and B- lymphocyte function.

Shingles: See herpes zoster.

Side Effect: Undesirable reaction resulting from immunization.

Smallpox: An acute, highly infectious, often fatal disease caused by a poxvirus and characterized by high fever and aches with subsequent widespread eruption of pimples that blister, produce pus, and form pockmarks. Also called *variola*.

Strain: A specific version of an organism. Many diseases, including HIV/AIDS and hepatitis, have multiple strains.

Subclinical infection: The presence of infection without symptoms. Also known as inapparent or asymptomatic infection.

Sudden Infant Death Syndrome (SIDS): The sudden and unexpected death of a healthy infant under 1 year of age. A diagnosis of SIDS is made when an autopsy cannot determine another cause of death. The cause of SIDS is unknown. Also known as "crib" or "cot" death.

Susceptible: Unprotected against disease.

Т

Temporal association: Two or more events that occur around the same time but may be unrelated, chance occurrences.

Teratogenic: Listen ([MP3]

Of, relating to, or causing developmental malformations.

Tetanus: Listen **()** [MP3]

Toxin-producing bacterial disease marked by painful muscle spasms.

Thimerosal: Listen ([MP3]

Thimerosal is a mercury-containing preservative used in some vaccines and other products since the 1930's. There is no convincing evidence of harm caused by the low concentrations of thimerosal in vaccines, except for minor reactions like redness and swelling at the injection site. However, in July 1999, the Public Health Service agencies, the American Academy of Pediatrics, and vaccine manufacturers agreed that thimerosal should be reduced or eliminated in vaccines as a precautionary measure. Today, all routinely recommended childhood vaccines manufactured for the U.S. market contain either no thimerosal or only trace amounts with the exception of some flu vaccines. There are thimerosal-free influenza vaccines available.

Exhibit 232

Case 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 13 of 497 Typhoid Fever: Typhoid fever is a life-threatening illness caused by the bacterium Salmonella Typhi. Persons with typhoid fever carry the bacteria in their bloodstream and intestinal tract.

Titer: Listen (MP3)

The detection of antibodies in blood through a laboratory test.

Transverse Myelitis: Listen ([MP3]

The sudden onset of spinal cord disease. Symptoms include general back pain followed by weakness in the feet and legs that moves upward. There is no cure and many patients are left with permanent disabilities or paralysis. Transverse Myelitis is a demyelinating disorder that may be associated with Multiple Sclerosis (MS). Also see demyelinating disorders.

IJ

Urticaria: Listen (MP3)

The eruption of red marks on the skin that are usually accompanied by itching. This condition can be caused by an allergy (e.g. to food or drugs), stress, infection or physical agents (e.g. heat or cold). Also known as hives.

V

Vaccination: Listen (MP3)

Injection of a killed or weakened infectious organism in order to prevent the disease.

Vaccinia: Listen (MP3)

A virus related to the smallpox and cowpox viruses, which is used in smallpox vaccine.

Vaccine: Listen ([MP3]

A product that produces immunity therefore protecting the body from the disease. Vaccines are administered through needle injections, by mouth and by aerosol.

Vaccine Adverse Event Reporting System (VAERS): A database managed by the Centers for Disease Control and Prevention and the Food and Drug Administration. VAERS provides a mechanism for the collection and analysis of adverse events associated with vaccines currently licensed in the United States. Reports to VAERS 🗹 can be made by the vaccine manufacturer, recipient, their parent/guardian or health care provider. For more information on VAERS call (800) 822-7967.

Vaccine Safety Datalink Project (VSD): In order to increase knowledge about vaccine adverse events, the Centers for Disease Control and Prevention have formed partnerships with eight large Health Management Organizations (HMOs) to continually evaluate vaccine safety. The project contains data on more than 6 million people. Medical records are monitored for potential adverse events following immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypothesis.

Varicella: Listen (MP3)

(Chickenpox) — An acute contagious disease characterized by papular and vesicular lesions.

Variola: Listen ([MP3]

See smallpox.

Vesicular: Listen (MP3)

Characterized by small elevations of the skin containing fluid (blisters).

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Viremia: Listen ([MP3]

The presence of a virus in the blood.

Virulence: Listen (MP3)

The relative capacity of a pathogen to overcome body defenses.

Virus: A tiny organism that multiplies within cells and causes disease such as chickenpox, measles, mumps, rubella, pertussis and hepatitis. Viruses are not affected by antibiotics, the drugs used to kill bacteria.

W

Waning Immunity: The loss of protective antibodies over time.

Whooping Cough: See Pertussis.

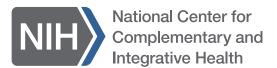
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EXHIBIT 233

U.S. Department of Health and Human Services National Institutes of Health



Placebo Effect

The "gold standard" for testing interventions in people is the "randomized, placebo-controlled" clinical trial, in which volunteers are randomly assigned to a test group receiving the experimental intervention or a control group receiving a placebo (an inactive substance that looks like the drug or treatment being tested). Comparing results from the two groups suggests whether changes in the test group result from the treatment or occur by chance.

The placebo effect is a beneficial health outcome resulting from a person's anticipation that an intervention will help. How a health care provider interacts with a patient also may bring about a positive response that's independent of any specific treatment.

Research supported by NCCIH has explored several aspects of the placebo effect. One study identified a genetic marker that may predict whether someone will respond to a placebo, another supported the idea that placebo responses may occur outside of conscious awareness, and a third suggested that placebos may be helpful even if patients know they're receiving placebos.

- Spotlighted Research Results
- What Is a Placebo? Q and A with Ted Kaptchuk

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EXHIBIT 234

placebo effect

DICTIONARY

THESAURUS

placebo effect noun



Definition of placebo effect

: improvement in the condition of a patient that occurs in response to treatment but cannot be considered due to the specific treatment used

Examples of placebo effect in a Sentence

Recent Examples on the Web

// The placebo effect can be strong, since parents typically want to see improvements.

Nicola Jones, New York Times, "Should You Give Your Kid CBD?,"
 30 Apr. 2020

// Yet every doctor knows the *placebo effect* is real; the mind can change what's happening in the body.

 Mary Hadar, Washington Post, "'Miracle' cures that hold lessons for Western medicine," 6 Mar. 2020

These example sentences are selected automatically from various online news sources to reflect current usage of the word 'placebo effect.' Views expressed in the examples do not represent the opinion of Merriam-Webster or its editors. Send us feedback.



EXHIBIT 235

Vaccines Licensed for Use in the United States

| Product Name | Trade Name |
|--|---------------|
| Adenovirus Type 4 and Type 7 Vaccine, Live, Oral (/vaccines-blood-biologics/approved-products/adenovirus-type-4-and-type-7-vaccine-live-oral) | No Trade Name |
| Anthrax Vaccine Adsorbed (/vaccines-blood-biologics/approved-products/anthrax-vaccine-adsorbed) | Biothrax |
| BCG Live (/vaccines-blood-biologics/approved-products/bcg-live) | BCG Vaccine |
| BCG Live (/vaccines-blood-biologics/approved-products/bcg-live) | TICE BCG |
| Cholera Vaccine Live Oral (/vaccines-blood-biologics/approved-products/vaxchora) | Vaxchora |
| Dengue Tetravalent Vaccine, Live (/vaccines-blood-biologics/dengvaxia) | DENGVAXIA |
| Diphtheria & Tetanus Toxoids Adsorbed (/vaccines-blood-biologics/approved-products/diphtheria-and-tetanus-toxoids-adsorbed) | No Trade Name |
| Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed (/vaccines-blood-biologics/approved-products/infanrix) | Infanrix |
| Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed (/vaccines-blood-biologics/approved-products/daptacel) | DAPTACEL |
| Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed, Hepatitis B (recombinant) and Inactivated Poliovirus Vaccine Combined (/vaccines-blood-biologics/approved-products/diphtheria-and-tetanus-toxoids-and-acellular-pertussis-adsorbed-hepatitis-b-recombinant-and) | Pediarix |
| Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine (/vaccines-blood-biologics/approved-products/diphtheria-and-tetanus-toxoids-and-acellular-pertussis-adsorbed-and-inactivated-poliovirus-vaccine) | KINRIX |
| Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine (/vaccines-blood-biologics/approved-products/diphtheria-and-tetanus-toxoids-and-acellular-pertussis-adsorbed-and-inactivated-poliovirus-vaccine) | Quadracel |
| Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (/vaccines-blood-biologics/vaxelis) | VAXELIS |
| Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and | Pentacel |

Exhibit 235

Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (/vaccines-bloodbiologics/approxed-products/diphthenia and tetanus to cold so the products of inactivated-poliovirus-and)

| Ebola Zaire Vaccine, Live (/vaccines-blood-biologics/ervebo) | ERVEBO |
|---|---------------|
| Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) (/vaccines-blood-biologics/approved-products/haemophilus-b-conjugate-vaccine-meningococcal-protein-conjugate) | PedvaxHIB |
| Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (/vaccines-blood-biologics/approved-products/haemophilus-b-conjugate-vaccine-tetanus-toxoid-conjugate) | ActHIB |
| Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (/vaccines-blood-biologics/approved-products/hiberix) | Hiberix |
| Hepatitis A Vaccine, Inactivated (/vaccines-blood-biologics/approved-products/havrix) | Havrix |
| Hepatitis A Vaccine, Inactivated (/vaccines-blood-biologics/approved-products/vaqta) | VAQTA |
| Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine (/vaccines-blood-biologics/approved-products/twinrix) | Twinrix |
| Hepatitis B Vaccine (Recombinant) (/vaccines-blood-biologics/approved-products/recombivax-hb) | Recombivax HB |
| Hepatitis B Vaccine (Recombinant) (/vaccines-blood-biologics/approved-products/engerix-b) | Engerix-B |
| Hepatitis B Vaccine (Recombinant), Adjuvanted (/vaccines-blood-biologics/approved-products/heplisav-b) | HEPLISAV-B |
| Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant (/vaccines-blood biologics/approved-products/human-papillomavirus-vaccine) | l- Gardasil |
| Human Papillomavirus 9-valent Vaccine, Recombinant (/vaccines-blood-biologics/approved-products/gardasil-9) | Gardasil 9 |
| Human Papillomavirus Bivalent (Types 16, 18) Vaccine, Recombinant (/vaccines-blood-biologics/approved-products/cervarix) | Cervarix |
| Influenza A (H1N1) 2009 Monovalent Vaccine (/vaccines-blood-biologics/approved-products/influenza-h1n1-2009-monovalent-vaccine-csl-limited) | No Trade Name |
| Influenza A (H1N1) 2009 Monovalent Vaccine (/vaccines-blood-biologics/approved-products/influenza-h1n1-2009-monovalent-vaccine-medimmune-llc) | No Trade Name |
| Influenza A (H1N1) 2009 Monovalent Vaccine (/vaccines-blood-biologics/approved-products/influenza-h1n1-2009-monovalent-vaccine-id-biomedical-corporation-quebec) | No Trade Name |
| 2 | Exhibit 235 |

| Influenza A (H1N1) 2009 Monovalent Vaccine (/vaccines-blood-biologics/approved-products/influenza-h1ri102609917670vallent-vaccine-novartis-vaccines-land-diagnostics-linited)2 | No Trade Name of 497 |
|--|---|
| Influenza A (H1N1) 2009 Monovalent Vaccine (/vaccines-blood-biologics/approved-products/influenza-h1n1-2009-monovalent-vaccine-sanofi-pasteur-inc) | No Trade Name |
| Influenza Virus Vaccine, H5N1 (/vaccines-blood-biologics/approved-products/influenza-virus-vaccine-h5n1-national-stockpile) (for National Stockpile) | No Trade Name |
| Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (/vaccines-blood-biologics/approved-products/influenza-h5n1-virus-monovalent-vaccine-adjuvanted) | No Trade Name |
| Influenza A (H5N1) Monovalent Vaccine, Adjuvanted (/vaccines-blood-biologics/audenz) | AUDENZ |
| Influenza Vaccine, Adjuvanted (/vaccines-blood-biologics/fluad-quadrivalent) | FLUAD QUADRIVALENT |
| Influenza Vaccine, Adjuvanted (/vaccines-blood-biologics/approved-products/fluad) | FLUAD |
| Influenza Vaccine (/vaccines-blood-biologics/approved-products/afluria-quadrivalent) | AFLURIA QUADRIVALENT |
| Influenza Vaccine (/vaccines-blood-biologics/approved-products/flucelvax-quadrivalent) | Flucelvax Quadrivalent |
| Influenza Virus Vaccine (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/afluria) | Afluria |
| Influenza Virus Vaccine (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/flulaval) | FluLaval |
| Influenza Vaccine, Live, Intranasal (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/flumist) | FluMist |
| Influenza Virus Vaccine (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/fluarix) | Fluarix |
| Influenza Virus Vaccine (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/fluvirin) | Fluvirin |
| Influenza Virus Vaccine (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/agriflu) | Agriflu |
| Influenza Virus Vaccine (Trivalent, Types A and B) (/vaccines-blood-biologics/approved-products/fluzone-fluzone-high-dose-and-fluzone-intradermal) | Fluzone, Fluzone High- Dose and Fluzone Intradermal |
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| Influenza Virus Vaccine (Trivalent, Types A and B) (Vaccines bloods biologics approved products flucely ax) Page 23 of | Flucelvax 497 |
|---|--------------------------|
| Influenza Vaccine (Trivalent) (/vaccines-blood-biologics/approved-products/flublok) | Flublok |
| Influenza Vaccine (Quadrivalent) (/vaccines-blood-biologics/approved-products/flublok-quadrivalent) | Flublok Quadrivalent |
| Influenza Vaccine,Live, Intranasal (Quadrivalent, Types A and Types B) (/vaccines-blood-biologics/approved-products/flumist-quadrivalent) | FluMist Quadrivalent |
| Influenza Virus Vaccine (Quadrivalent, Types A and Types B) (/vaccines-blood-biologics/approved-products/fluarix-quadrivalent) | Fluarix Quadrivalent |
| Influenza Virus Vaccine (Quadrivalent, Types A and Types B) (/vaccines-blood-biologics/approved-products/fluzone-quadrivalent) | Fluzone Quadrivalent |
| Influenza Vaccine (/vaccines-blood-biologics/approved-products/flulaval-quadrivalent) | Flulaval Quadrivalent |
| Japanese Encephalitis Virus Vaccine, Inactivated, Adsorbed (/vaccines-blood-biologics/approved-products/japanese-encephalitis-vaccine-inactivated-adsorbed) | lxiaro |
| Measles, Mumps, and Rubella Virus Vaccine, Live (/vaccines-blood-biologics/approved-products/measles-mumps-and-rubella-virus-vaccine-live) | M-M-R II |
| Measles, Mumps, Rubella and Varicella Virus Vaccine Live (/vaccines-blood-biologics/approved-products/measles-mumps-rubella-and-varicella-virus-vaccine-live) | ProQuad |
| Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (/vaccines-blood-biologics/approved-products/menveo) | Menveo |
| Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (/vaccines-blood-biologics/approved-products/meningococcal-groups-c-y-and-w-135-polysaccharide-diphtheria-toxoid-conjugate-vaccine) | Menactra |
| Meningococcal Group B Vaccine (/vaccines-blood-biologics/approved-products/bexsero) | BEXSERO |
| Meningococcal Group B Vaccine (/vaccines-blood-biologics/approved-products/trumenba) | TRUMENBA |
| Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined (/vaccines-blood-biologics/approved-products/meningococcal-polysaccharide-vaccine-groups-c-y-and-w-135-combined) | Menomune- A/C/Y/W-135 |
| Meningococcal (Groups A, C, Y, W) Conjugate Vaccine (/vaccines-blood-biologics/menquadfi) | MenQuadfi |

Plague Vaccine No trade name

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Pneumococcal Vaccine, Polyvalent (/vaccines-blood-biologics/approved-products/pneumococcal-vaccine-polyvalent)

Pneumococcal Vaccine, Polyvalent (/vaccines-blood-biologics/approved-products/pneumococcal-vaccine-polyvalent)

Pneumococcal 13-valent Conjugate Vaccine (/vaccines-blood-biologics/approved-products/pneumococcal-13-valent-conjugate-vaccine-diphtheria-crm197-protein) (Diphtheria CRM₁₉₇ Protein)

Prevnar 13

Poliovirus Vaccine Inactivated (Human Diploid Cell)

Poliovax

Poliovirus Vaccine Inactivated (Monkey Kidney Cell) (/vaccines-blood-biologics/approved-products/poliovirus-vaccine-inactivated-monkey-kidney-cell)

IPOL

Rabies Vaccine (/vaccines-blood-biologics/approved-products/rabies-vaccine)

Imovax

Rabies Vaccine (/vaccines-blood-biologics/approved-products/rabavert-rabies-vaccine)

RabAvert

Rabies Vaccine Adsorbed

No Trade Name

Rotavirus Vaccine, Live, Oral (/vaccines-blood-biologics/approved-products/rotavirus-vaccine-live-oral)

ROTARIX

Rotavirus Vaccine, Live, Oral, Pentavalent (/vaccines-blood-biologics/approved-products/rotateq)

RotaTeq

Smallpox and Monkeypox Vaccine, Live, Non-Replicating (/vaccines-blood-biologics/jynneos)

JYNNEOS

Smallpox (Vaccinia) Vaccine, Live (/vaccines-blood-biologics/approved-products/smallpox-vaccinia-vaccine-live)

ACAM2000

Tetanus & Diphtheria Toxoids, Adsorbed (/vaccines-blood-biologics/approved-products/tetanus-diphtheria-toxoids-adsorbed)

TDVAX

Tetanus & Diphtheria Toxoids Adsorbed for Adult Use (/vaccines-blood-biologics/approved-products/tenivac)

TENIVAC

Tetanus Toxoid Adsorbed (/vaccines-blood-biologics/approved-products/diphtheria-and-tetanus-toxoids-adsorbed)

No Trade Name

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (/vaccines-blood-biologics/approved-products/tetanus-toxoid-reduced-diphtheria-toxoid-and-acellular-pertussis-vaccine-adsorbed)

Adacel

Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (/vaccines-blood-biologics/approved-products/tetanus-toxoid-reduced-diphtheria-toxoid-and-acellular-pertussis-vaccine-adsorbed)

Boostrix

Typhoid Vaccine Live Oral Ty21a (/vaccines-blood-biologics/approved-products/vivotif)

Vivotif

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|---|----------|
| Varicella Virus Vaccine Live (/vaccines-blood-biologics/approved-products/varivax) | Varivax |
| Yellow Fever Vaccine (/vaccines-blood-biologics/approved-products/yellow-fever-vaccine) | YF-Vax |
| Zoster Vaccine, Live, (Oka/Merck) (/vaccines-blood-biologics/approved-products/zoster-vaccine-live) | Zostavax |
| Zoster Vaccine Recombinant, Adjuvanted (/vaccines-blood-biologics/vaccines/shingrix) | SHINGRIX |

EXHIBIT 236

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These highlights do not include all the information needed to use INFANRIX safely and effectively. See full prescribing information for INFANRIX.

INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) Suspension for Intramuscular Injection Initial U.S. Approval: 1997

----INDICATIONS AND USAGE ---

INFANRIX is a vaccine indicated for active immunization against diphtheria, tetanus, and pertussis as a 5-dose series in infants and children aged 6 weeks through 6 years (prior to the 7th birthday). (1)

---DOSAGE AND ADMINISTRATION -

A 0.5-mL intramuscular injection given as a 5-dose series: (2.2)

- One dose each at 2, 4, and 6 months of age.
- One booster dose at 15 to 20 months of age and another booster dose at 4 to 6 years of age.

--- DOSAGE FORMS AND STRENGTHS--

Single-dose vials and single-dose, prefilled syringes containing a 0.5-mL suspension for injection. (3)

----CONTRAINDICATIONS ----

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, or pertussis-containing vaccine, or to any component of INFANRIX. (4.1)
- Encephalopathy within 7 days of administration of a previous pertussiscontaining vaccine. (4.2)
- Progressive neurologic disorders. (4.3)

---- WARNINGS AND PRECAUTIONS ----

- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give INFANRIX should be based on potential benefits and risks. (5.1)
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.2)

- 9 Filed 12/29/20 Page 27 of 497 Syncope (fainting) can occur in association with administration of injectable vaccines, including INFANRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)
- If temperature ≥105°F, collapse or shock-like state, or persistent, inconsolable crying lasting ≥3 hours have occurred within 48 hours after receipt of a pertussis-containing vaccine, or if seizures have occurred within 3 days after receipt of a pertussis-containing vaccine, the decision to give INFANRIX should be based on potential benefits and risks. (5.4)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with INFANRIX. (5.5)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including INFANRIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.6)

--ADVERSE REACTIONS--

Rates of injection site reactions (pain, redness, swelling) ranged from 10% to 53%, depending on reaction and dose number, and were highest following Doses 4 and 5. Fever was common (20% to 30%) following Doses 1-3. Other common solicited adverse reactions were drowsiness, irritability/fussiness, and loss of appetite, reported in approximately 15% to 60% of subjects, depending on reactions and dose number. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Glax oS mith Kline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

--- DRUG INTERACTIONS--

Do not mix INFANRIX with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/XXXX

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Preparation for Administration
 - 2.2 Dose and Schedule
 - 2.3 Use of INFANRIX with Other DTaP Vaccines
 - 2.4 Additional Dosing Information
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
 - 4.1 Hypersensitivity
 - 4.2 Encephalopathy
 - 4.3 Progressive Neurologic Disorder

5 WARNINGS AND PRECAUTIONS

- 5.1 Guillain-Barré Syndrome
 - 5.2 Latex
 - 5.3 Syncope
- 5.4 Adverse Reactions following Prior Pertussis Vaccination
- 5.5 Children at Risk for Seizures
- 5.6 Apnea in Premature Infants
- 5.7 Preventing and Managing Allergic Vaccine Reactions
- ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience

- 6.2 Postmarketing Experience
- DRUG INTERACTIONS
 - 7.1 Concomitant Vaccine Administration
 - 7.2 Immunosuppressive Therapies
- 8 USE IN SPECIFIC POPULATIONS
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- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
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- 14 CLINICAL STUDIES
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 - 14.2 Pertussis
 - 14.3 Immune Response to Concomitantly Administered Vaccines
- 15 REFERENCES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

^{*}Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INFANRIX is indicated for active immunization against diphtheria, tetanus, and pertussis as a 5-dose series in infants and children aged 6 weeks through 6 years (prior to the 7th birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.2 Dose and Schedule

A 0.5-mL dose of INFANRIX is approved for intramuscular administration in infants and children aged 6 weeks through 6 years (prior to the 7th birthday) as a 5-dose series. The series consists of a primary immunization course of 3 doses administered at 2, 4, and 6 months of age (at intervals of 4 to 8 weeks), followed by 2 booster doses, administered at 15 to 20 months of age and at 4 to 6 years of age. The first dose may be given as early as 6 weeks of age.

The preferred administration site is the anterolateral aspect of the thigh for most infants aged younger than 12 months and the deltoid muscle of the upper arm for most children aged 12 months through 6 years.

2.3 Use of INFANRIX with Other DTaP Vaccines

Sufficient data are not available on the safety and effectiveness of interchanging INFANRIX and Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) vaccines from different manufacturers for successive doses of the DTaP vaccination series. Because the pertussis antigen components of INFANRIX and PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] are the same, INFANRIX may be used to complete a DTaP vaccination series initiated with PEDIARIX.

2.4 Additional Dosing Information

If any recommended dose of pertussis vaccine cannot be given [see Contraindications (4.2, 4.3), Warnings and Precautions (5.5)], Diphtheria and Tetanus Toxoids Adsorbed (DT) For Pediatric Use should be given according to its prescribing information.

3 DOSAGE FORMS AND STRENGTHS

INFANRIX is a suspension for injection available in 0.5-mL single-dose vials and 0.5-mL single-dose, prefilled TIP-LOK syringes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid, tetanus toxoid-, or pertussis-containing vaccine, or to any component of INFANRIX is a contraindication [see Description (11)]. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if immunization with any of these components is being considered.

4.2 Encephalopathy

Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause is a contraindication to administration of any pertussis-containing vaccine, including INFANRIX.

4.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy, is a contraindication to administration of any pertussis-containing vaccine, including INFANRIX. Pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established and the condition has stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including INFANRIX, should be based on careful consideration of the potential benefits and possible risks. When a decision is made to withhold tetanus toxoid, other available vaccines should be given, as indicated.

5.2 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic

reactions.

5.3 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including INFANRIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.4 Adverse Reactions following Prior Pertussis Vaccination

If any of the following reactions occur in temporal relation to receipt of a pertussis-containing vaccine, the decision to give any pertussis-containing vaccine, including INFANRIX, should be based on careful consideration of the potential benefits and possible risks:

- Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

5.5 Children at Risk for Seizures

For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a pertussis-containing vaccine, including INFANRIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

5.6 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including INFANRIX, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

5.7 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine hypersensitivity. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

Approximately 95,000 doses of INFANRIX have been administered in clinical studies. In these

studies, 29,243 infants have received INFANRIX in primary series studies: 6,081 children have received a fourth consecutive dose of INFANRIX, 1,764 children have received a fifth consecutive dose of INFANRIX, and 559 children have received a dose of INFANRIX following 3 doses of PEDIARIX.

Solicited Adverse Reactions

In a U.S. study, 335 infants received INFANRIX, ENGERIX-B [Hepatitis B Vaccine (Recombinant)], inactivated poliovirus vaccine (IPV, Sanofi Pasteur SA), Haemophilus b (Hib) conjugate vaccine (Wyeth Pharmaceuticals Inc.), and pneumococcal 7-valent conjugate (PCV7) vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited local reactions and general adverse reactions were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days) (Table 1). Among subjects, 69% were white, 16% were Hispanic, 8% were black, 4% were Asian, and 2% were of other racial/ethnic groups.

Table 1. Solicited Local and General Adverse Reactions (%) Occurring within 4 Days of Vaccination^a with Separate Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Haemophilus b (Hib) Conjugate Vaccine, and Pneumococcal Conjugate Vaccine (PCV7) (Modified Intent-to-Treat Cohort)

| (1CV) (Modified Intent-to-11eat) | INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7 | | |
|--------------------------------------|---|--------|--------|
| Adverse Reaction | Dose 1 | Dose 2 | Dose 3 |
| Local ^b | | | |
| n | 335 | 323 | 315 |
| Pain, any | 32 | 30 | 30 |
| Pain, Grade 2 or 3 | 9 | 9 | 9 |
| Pain, Grade 3 | 3 | 2 | 1 |
| Redness, any | 18 | 33 | 39 |
| Redness, >20 mm | 0 | 0 | 2 |
| Swelling, any | 10 | 20 | 25 |
| Swelling, >20 mm | 1 | 0 | 1 |
| General | | | |
| n | 333 | 321 | 311 |
| Fever ^c (≥100.4°F) | 20 | 30 | 24 |
| Fever ^c (>101.3°F) | 5 | 8 | 6 |
| Fever ^c (>102.2°F) | 0 | 3 | 2 |
| Fever ^c (>103.1°F) | 0 | 0 | 0 |
| n | 335 | 323 | 315 |
| Drowsiness, any | 54 | 48 | 38 |
| Drowsiness, Grade 2 or 3 | 18 | 12 | 11 |
| Drowsiness, Grade 3 | 4 | 1 | 2 |
| Irritability/Fussiness, any | 62 | 62 | 57 |
| Irritability/Fussiness, Grade 2 or 3 | 19 | 21 | 19 |
| Irritability/Fussiness, Grade 3 | 4 | 3 | 3 |
| Loss of appetite, any | 28 | 27 | 24 |
| Loss of appetite, Grade 2 or 3 | 5 | 3 | 5 |
| Loss of appetite, Grade 3 | 1 | 0 | 0 |

Hib conjugate vaccine and PCV7 manufactured by Wyeth Pharmaceuticals Inc. IPV manufactured by Sanofi Pasteur SA.

Modified intent-to-treat cohort = All vaccinated subjects for whom safety data were available. n = Number of infants for whom at least one symptom sheet was completed; for fever; numbers exclude missing temperature recordings or tympanic measurements.

Grade 2: Pain defined as cried/protested on touch; drowsiness defined as interfered with normal daily activities; irritability/fussiness defined as crying more than usual/interfered with normal daily activities; loss of appetite defined as eating less than usual/interfered with normal daily activities.

Grade 3: Pain defined as cried when limb was moved/spontaneously painful; drowsiness defined

as prevented normal daily activities; irritability/fussiness defined as crying that could not be comforted/prevented normal daily activities; loss of appetite defined as no eating at all.

- ^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.
- ^b Local reactions at the injection site for INFANRIX.
- ^c Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive equivalent rectal temperature.

In a U.S. study, the safety of a booster dose of INFANRIX was evaluated in children aged 15 to 18 months whose previous 3 DTaP doses were with INFANRIX (n = 251) or PEDIARIX (n = 559). Vaccines administered concurrently with the fourth dose of INFANRIX included measles, mumps, and rubella (MMR) vaccine (Merck & Co., Inc.), varicella vaccine (Merck & Co., Inc.), pneumococcal 7-valent conjugate (PCV7) vaccine (Wyeth Pharmaceuticals Inc.), and any U.S.-licensed Hib conjugate vaccine; these were given concomitantly in 13.2%, 6.3%, 37.4%, and 41.2% of subjects, respectively. Data on solicited adverse reactions were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days) (Table 2). Among subjects, 85% were white, 6% were Hispanic, 6% were black, 1% were Asian, and 2% were of other racial/ethnic groups.

Table 2. Solicited Local and General Adverse Reactions (%) Occurring within 4 Days of Vaccination^a with INFANRIX Administered as the Fourth Dose following 3 Previous Doses

of INFANRIX or PEDIARIX (Total Vaccinated Cohort)

| | Group Primed with INFANRIX ^b | Group Primed with PEDIARIX ^c |
|---|---|---|
| Adverse Reaction | n = 247 | n = 553 |
| Locald | | |
| Pain, any | 45 | 48 |
| Pain, Grade 2 or 3 | 19 | 19 |
| Pain, Grade 3 | 4 | 3 |
| Redness, any | 48 | 50 |
| Redness, >20 mm | 6 | 6 |
| Swelling, any | 33 | 33 |
| Swelling, >20 mm | 4 | 5 |
| Increase in mid-thigh circumference, any | 33 | 26 |
| Increase in mid-thigh circumference, >40 mm | 0 | 1 |
| General | | |
| Fever ^e (>99.5°F) | 9 | 15 |
| Fever ^e (>100.4°F) | 5 | 7 |
| Fever ^e (>101.3°F) | 2 | 2 |
| Drowsiness, any | 36 | 31 |
| Drowsiness, Grade 2 or 3 | 9 | 7 |
| Drowsiness, Grade 3 | 2 | 1 |
| Irritability, any | 52 | 54 |
| Irritability, Grade 2 or 3 | 18 | 20 |
| Irritability, Grade 3 | 3 | 1 |
| Loss of appetite, any | 25 | 23 |
| Loss of appetite, Grade 2 or 3 | 5 | 5 |
| Loss of appetite, Grade 3 | 2 | 0 |

Total Vaccinated Cohort = All subjects who received a dose of study vaccine.

Grade 2: Pain defined as cried/protested on touch; drowsiness defined as interfered with normal daily activities; irritability defined as crying more than usual/interfered with normal daily activities; loss of appetite defined as eating less than usual/no effect on normal daily activities. Grade 3: Pain defined as cried when limb was moved/spontaneously painful; drowsiness defined as prevented normal daily activities; irritability defined as crying that could not be comforted/prevented normal daily activities; loss of appetite defined as eating less than usual/interfered with normal daily activities.

n = Number of subjects for whom at least one symptom sheet was completed.

^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

^b Received INFANRIX, ENGERIX-B, IPV (Sanofi Pasteur SA), PCV7 vaccine (Wyeth

Pharmaceuticals Inc.), and Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age.

- ^c Received PEDIARIX, PCV7 vaccine (Wyeth Pharmaceuticals Inc.), and Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age or PCV7 vaccine 2 weeks later.
- ^d Local reactions at the injection site for INFANRIX.
- ^e Axillary temperatures.

In a U.S. study, the safety of a fifth consecutive dose of INFANRIX coadministered at separate sites with a fourth dose of IPV (Sanofi Pasteur SA) and a second dose of MMR vaccine (Merck & Co., Inc.) was evaluated in 1,053 children aged 4 to 6 years. Data on solicited adverse reactions were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days) (Table 3). Among subjects, 43% were white, 18% Hispanic, 15% Asian, 7% black, and 17% were of other racial/ethnic groups.

Table 3. Solicited Local and General Adverse Reactions (%) Occurring within 4 Days of Vaccination^a with a Fifth Consecutive Dose of INFANRIX when Coadministered with IPV and MMR Vaccine (Total Vaccinated Cohort)

| Local ^b | n = 1,039-1,043 |
|--|-----------------|
| Pain, any | 53 |
| Pain, Grade 2 or 3 ^c | 12 |
| Pain, Grade 3 ^c | 1 |
| Redness, any | 37 |
| Redness, ≥50 mm | 20 |
| Redness, ≥110 mm | 4 |
| Arm circumference increase, any | 38 |
| Arm circumference increase, >20 mm | 7 |
| Arm circumference increase, >30 mm | 3 |
| Swelling, any | 27 |
| Swelling, ≥50 mm | 12 |
| Swelling, ≥110 mm | 2 |
| General | n = 993-1,036 |
| Drowsiness, any | 18 |
| Drowsiness, Grade 3 ^d | 1 |
| Fever, ≥99.5°F | 15 |
| Fever, >100.4°F | 4 |
| Fever, >102.2°F | 1 |
| Fever, >104°F | 0 |
| Loss of appetite, any | 16 |
| Loss of appetite, Grade 3 ^e | 1 |

IPV manufactured by Sanofi Pasteur SA. MMR vaccine manufactured by Merck & Co., Inc. Total Vaccinated Cohort = All vaccinated subjects for whom safety data were available.

In the U.S. booster immunization studies in which INFANRIX was administered as the fourth or fifth dose in the DTaP series following previous doses with INFANRIX or PEDIARIX, large swelling reactions of the limb injected with INFANRIX were assessed.

In the fourth-dose study, a large swelling reaction was defined as injection site swelling with a diameter of >50 mm, a >50 mm increase in the mid-thigh circumference compared with the pre-

n = Number of children with evaluable data for the reactions listed.

^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

^b Local reactions at the injection site for INFANRIX.

^c Grade 2 defined as painful when the limb was moved; Grade 3 defined as preventing normal daily activities.

^d Grade 3 defined as preventing normal daily activities.

e Grade 3 defined as not eating at all.

vaccination measurement, and/or any diffuse swelling that interfered with or prevented daily activities. The overall incidence of large swelling reactions occurring within 4 days (Day 0-Day 3) following INFANRIX was 2.3%.

In the fifth-dose study, a large swelling reaction was defined as swelling that involved >50% of the injected upper arm length and that was associated with a >30 mm increase in mid-upper arm circumference within 4 days following vaccination. The incidence of large swelling reactions following the fifth consecutive dose of INFANRIX was 1.0%.

Less Common and Serious General Adverse Reactions

Selected adverse reactions reported from a double-blind, randomized Italian clinical efficacy trial involving 4,696 children administered INFANRIX or 4,678 children administered whole-cell DTP vaccine (DTwP) (manufactured by Connaught Laboratories, Inc.) as a 3-dose primary series are shown in Table 4. The incidence of rectal temperature ≥104°F, hypotonic-hyporesponsive episodes, and persistent crying ≥3 hours following administration of INFANRIX was significantly less than that following administration of whole-cell DTP vaccine.

Table 4. Selected Adverse Reactions Occurring within 48 Hours following Vaccination with INFANRIX or Whole-Cell DTP in Italian Infants at 2, 4, or 6 Months of Age

| INTAINER OF WHOIC-CENDIT III Italian Illiants at 2, 4, of 6 Wonters of Age | | | | | | |
|--|-------------|--------------------|----------------|------------------------|--|--|
| | INF | INFANRIX | | Whole-Cell DTP Vaccine | | |
| | (n = 13, ') | (n = 13,761 Doses) | | 20 Doses) | | |
| | | Rate/1,000 | | Rate/1,000 | | |
| Reaction | Number | Doses | Number | Doses | | |
| Fever (≥104°F) ^{a,b} | 5 | 0.36 | 32 | 2.4 | | |
| Hypotonic-hyporesponsive episode ^c | 0 | 0 | 9 | 0.67 | | |
| Persistent crying ≥3 hours ^a | 6 | 0.44 | 54 | 4.0 | | |
| Seizures ^d | 1e | 0.07 | 3 ^f | 0.22 | | |

a *P* < 0.001.

In a German safety study that enrolled 22,505 infants (66,867 doses of INFANRIX administered as a 3-dose primary series at 3, 4, and 5 months of age), all subjects were monitored for unsolicited adverse events that occurred within 28 days following vaccination using report cards. In a subset of subjects (n = 2,457), these cards were standardized diaries which solicited specific adverse reactions that occurred within 8 days of each vaccination in addition to unsolicited adverse events which occurred from enrollment until approximately 30 days following the third vaccination. Cards from the whole cohort were returned at subsequent visits and were

^b Rectal temperatures.

 $^{^{\}circ} P = 0.002.$

^d Not statistically significant at P < 0.05.

^e Maximum rectal temperature within 72 hours of vaccination = 103.1°F.

f Maximum rectal temperature within 72 hours of vaccination = 99.5°F, 101.3°F, and 102.2°F.

supplemented by spontaneous reporting by parents and a medical history after the first and second doses of vaccine. In the subset of 2,457, adverse events following the third dose of vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit. Adverse events in the remainder of the cohort were reported via report cards which were returned by mail approximately 28 days after the third dose of vaccine. Adverse reactions (rates per 1,000 doses) occurring within 7 days following any of the first 3 doses included: unusual crying (0.09), febrile seizure (0.0), afebrile seizure (0.13), and hypotonic-hyporesponsive episodes (0.01).

6.2 Postmarketing Experience

In addition to reports in clinical trials for INFANRIX, the following adverse reactions have been identified during postapproval use of INFANRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

Infections and Infestations

Bronchitis, cellulitis, respiratory tract infection.

Blood and Lymphatic System Disorders

Lymphadenopathy, thrombocytopenia.

Immune System Disorders

Anaphylactic reaction, hypersensitivity.

Nervous System Disorders

Encephalopathy, headache, hypotonia, syncope.

Ear and Labyrinth Disorders

Ear pain.

Cardiac Disorders

Cyanosis.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, cough.

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema, pruritus, rash, urticaria.

General Disorders and Administration Site Conditions

Fatigue, injection site induration, injection site reaction, Sudden Infant Death Syndrome.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

In clinical trials, INFANRIX was given concomitantly with Hib conjugate vaccine, pneumococcal 7-valent conjugate vaccine, hepatitis B vaccine, IPV, and the second dose of MMR vaccine [see Adverse Reactions (6.1), Clinical Studies (14.3)].

When INFANRIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes. INFANRIX should not be mixed with any other vaccine in the same syringe or vial.

7.2 Immunos uppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to INFANRIX.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of INFANRIX in infants aged younger than 6 weeks and children aged 7 to 16 years have not been established. INFANRIX is not approved for use in these age groups.

11 DESCRIPTION

INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is a noninfectious, sterile vaccine for intramuscular administration. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis toxin (PT), 25 mcg of filamentous hemagglutinin (FHA), and 8 mcg of pertactin (69 kiloDalton outer membrane protein).

The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* (*C. diphtheriae*) in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* (*C. tetani*) in a modified Latham medium derived from bovine casein. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor present an undue risk for bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* (*B. pertussis*) culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

Diphtheria and tetanus toxoids and pertussis antigens (PT, FHA, and pertactin) are individually adsorbed onto aluminum hydroxide.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice.

Each 0.5-mL dose contains aluminum hydroxide as adjuvant (not more than 0.625 mg aluminum by assay) and 4.5 mg of sodium chloride. Each dose also contains \leq 100 mcg of residual formaldehyde and \leq 100 mcg of polysorbate 80 (Tween 80).

INFANRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

INFANRIX is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection; a level of 0.1 IU/mL is regarded as protective.¹

Tetanus

Tetanus is an acute toxin-mediated infectious disease caused by a potent exotoxin released by *C. tetani*. Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.^{2,3} A level of 0.1 IU/mL is considered protective.⁴

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood. There is no well-established serological correlate of protection for pertussis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

INFANRIX has not been evaluated for carcinogenic or mutagenic potential or for impairment of

fertility.

14 CLINICAL STUDIES

14.1 Diphtheria and Tetanus

Efficacy of diphtheria toxoid used in INFANRIX was determined on the basis of immunogenicity studies. A VERO cell toxin-neutralizing test confirmed the ability of infant sera (N = 45), obtained one month after a 3-dose primary series, to neutralize diphtheria toxin. Levels of diphtheria antitoxin ≥ 0.01 IU/mL were achieved in 100% of the sera tested.

Efficacy of tetanus toxoid used in INFANRIX was determined on the basis of immunogenicity studies. An in vivo mouse neutralization assay confirmed the ability of infant sera (N = 45), obtained 1 month after a 3-dose primary series, to neutralize tetanus toxin. Levels of tetanus antitoxin ≥ 0.01 IU/mL were achieved in 100% of the sera tested.

14.2 Pertussis

Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.

A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial conducted in Italy assessed the absolute protective efficacy of INFANRIX when administered at 2, 4, and 6 months of age. The population used in the primary analysis of the efficacy of INFANRIX included 4,481 infants vaccinated with INFANRIX and 1,470 DT vaccinees. The mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine. After 3 doses, the absolute protective efficacy of INFANRIX against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76, 89). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be 71% (95% CI: 60, 78) against >7 days of any cough and 73% (95% CI: 63, 80) against ≥14 days of any cough. Vaccine efficacy after 3 doses and with no booster dose in the second year of life was assessed in 2 subsequent follow-up periods. A follow-up period from 24 months to a mean age of 33 months was conducted in a partially unblinded cohort (children who received DT were offered pertussis vaccine and those who declined were retained in the study cohort). During this period, the efficacy of INFANRIX against WHO-defined pertussis was 78% (95% CI: 62, 87). During the third follow-up period, which was conducted in an unblinded manner among children aged 3 to 6 years, the efficacy of INFANRIX against WHO-defined pertussis was 86% (95% CI: 79, 91). Thus, protection against pertussis in children administered 3 doses of INFANRIX in infancy was sustained to 6 years of age.

A prospective efficacy trial was also conducted in Germany employing a household contact study design. In preparation for this study, 3 doses of INFANRIX were administered at 3, 4, and 5 months of age to more than 22,000 children living in 6 areas of Germany in a safety and immunogenicity study. Infants who did not participate in the safety and immunogenicity study

could have received a DTwP vaccine or DT vaccine. Index cases were identified by spontaneous presentation to a physician. Households with at least one other member (i.e., besides index case) aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for incidence of pertussis by a physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 household contacts who had not received a pertussis vaccine, 96 developed WHO-defined pertussis, as compared with 7 of 112 contacts vaccinated with INFANRIX. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77, 95), with no indication of waning of protection up until the time of the booster vaccination. The average age of infants vaccinated with INFANRIX at the end of follow-up in this trial was 13 months (range: 6 to 25 months). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any cough was 67% (95% CI: 52, 78) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68, 89). The corresponding efficacy of INFANRIX against ≥14 days of any cough or paroxysmal cough were 73% (95% CI: 59, 82) and 84% (95% CI: 71, 91), respectively.

Pertussis Immune Response to INFANRIX Administered as a 3-Dose Primary Series

The immune responses to each of the 3 pertussis antigens contained in INFANRIX were evaluated in sera obtained 1 month after the third dose of vaccine in each of 3 studies (schedule of administration: 2, 4, and 6 months of age in the Italian efficacy study and one U.S. study; 3, 4, and 5 months of age in the German efficacy study). One month after the third dose of INFANRIX, the response rates to each pertussis antigen were similar in all 3 studies. Thus, although a serologic correlate of protection for pertussis has not been established, the antibody responses to these 3 pertussis antigens (PT, FHA, and pertactin) in a U.S. population were similar to those achieved in 2 populations in which efficacy of INFANRIX was demonstrated.

14.3 Immune Response to Concomitantly Administered Vaccines

In a U.S. study, INFANRIX was given concomitantly, at separate sites, with Hib conjugate vaccine (Sanofi Pasteur SA) at 2, 4, and 6 months of age. Subjects also received ENGERIX-B and oral poliovirus vaccine (OPV). One month after the third dose of Hib conjugate vaccine, 90% of 72 infants had anti-PRP (polyribosyl-ribitol-phosphate) ≥1.0 mcg/mL.

In a U.S. study, INFANRIX was given concomitantly, at separate sites, with ENGERIX-B, IPV (Sanofi Pasteur SA), pneumococcal 7-valent conjugate (PCV7), and Hib conjugate vaccines (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age. Immune responses were measured in sera obtained approximately 1 month after the third dose of vaccines. Among 121 subjects who had not received a birth dose of hepatitis B vaccine, 99.2% had anti-HBsAg (hepatitis B surface antigen) \geq 10 mIU/mL following the third dose of ENGERIX-B. Among 153 subjects, 100% had anti-poliovirus 1, 2, and 3, \geq 1:8 following the third dose of IPV. Although serological correlates for protection have not been established for the pneumococcal serotypes, a threshold level of

 \geq 0.3 mcg/mL was evaluated. Following the third dose of PCV7 vaccine, 91.8% to 99.4% of subjects (n = 146-156) had anti-pneumococcal polysaccharide \geq 0.3 mcg/mL for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 73.0% had a level \geq 0.3 mcg/mL for serotype 6B.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

INFANRIX is available in 0.5-mL single-dose vials and 0.5-mL single-dose, disposable, prefilled TIP-LOK syringes (packaged without needles):

NDC 58160-810-01 Vial in Package of 10: NDC 58160-810-11

NDC 58160-810-43 Syringe in Package of 10: NDC 58160-810-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

Provide the following information to the parent or guardian:

- Inform of the potential benefits and risks of immunization with INFANRIX, and of the importance of completing the immunization series.
- Inform about the potential for adverse reactions that have been temporally associated with administration of INFANRIX or other vaccines containing similar components.
- Instruct to report any adverse events to their healthcare provider.
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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INF:XXPI

EXHIBIT 237

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAPTACEL safely and effectively. See full prescribing information for DAPTACEL.

DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)

Suspension for Intramuscular Injection Initial U.S. Approval: 2002

-----INDICATIONS AND USAGE-----

 DAPTACEL is a vaccine indicated for active immunization against diphtheria, tetanus and pertussis as a five dose series in infants and children 6 weeks through 6 years of age (prior to 7th birthday). (1)

-----DOŚAGE AND ADMINISTRATION-----

 The five dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6 and 15-20 months of age, and at 4-6 years of age. (2.1, 2.2)

-----DOSAGE FORMS AND STRENGTHS-----

- Suspension for injection, supplied in single dose (0.5 mL) vials (3)
 - -----CONTRAINDICATIONS-----
- Severe allergic reaction (e.g. anaphylaxis) after a previous dose of any diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, or any component of DAPTACEL. (4.1)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)
- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

------WARNINGS AND PRECAUTIONS-----

- Carefully consider benefits and risks before administering DAPTACEL to persons with a history of:
 - fever ≥40.5°C (105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
 - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following DAPTACEL. (5.3)

- For infants and children with a history of previous seizures, an antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with DAPTACEL and for the next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including DAPTACEL, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.7)
- Syncope (fainting) has been reported following vaccination with DAPTACEL. Procedures should be in place to prevent falling injury and manage syncopal reactions. (5.8)

-----ADVERSE REACTIONS-----

Rates of adverse reactions varied by dose number, with systemic reactions most frequent following doses 1-3 and injection site reactions most frequent following doses 4 and 5. Systemic reactions that occurred in >50% of subjects following any dose included fussiness/irritability, inconsolable crying, and decreased activity/lethargy. Fever ≥38.0°C occurred in 6-16% of US subjects, depending on dose number. Injection site reactions that occurred in >30% of subjects following any dose included tenderness, redness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

-----DRUG INTERACTIONS-----

- In cases where DAPTACEL and Menactra are to be administered to children
 4 through 6 years of age, the two vaccines should be administered
 concomitantly or Menactra should be administered prior to DAPTACEL.
 Administration of Menactra one month after DAPTACEL has been shown to
 reduce meningococcal antibody responses to Menactra. (7.1)
- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may reduce the immune response to DAPTACEL. (7.2)

See 17 for PATIENT COUNSELING INFORMATION. Revised: [XX/201X]

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- 5.8 Syncope

6 ADVERSE REACTIONS

- 6.1 Data from Clinical Studies
- 6.2 Data from Post-Marketing Experience

DRUG INTERACTIONS

- 7.1 Concomitant Administration with Other Vaccines
- 7.2 Immunosuppressive Treatments

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
 11 **DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 13 NON-CLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Diphtheria
- 14.2 Tetanus
- 14.3 Pertussis
- 14.4 Concomitantly Administered Vaccines

15 REFERENCES

- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION
- Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

2 1 INDICATIONS AND USAGE

- 3 DAPTACEL® is a vaccine indicated for active immunization against diphtheria, tetanus and
- 4 pertussis as a five-dose series in infants and children 6 weeks through 6 years of age (prior to
- 5 seventh birthday).

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6 2 DOSAGE AND ADMINISTRATION

2.1 Immunization Series

- 8 DAPTACEL is to be administered as a 5 dose series at 2, 4 and 6 months of age (at intervals of 6-
- 9 8 weeks), at 15-20 months of age and at 4-6 years of age. The first dose may be given as early as
- 10 6 weeks of age. Four doses of DAPTACEL constitute a primary immunization course for
- pertussis. The fifth dose is a booster for pertussis immunization. Three doses of DAPTACEL
- 12 constitute a primary immunization course for diphtheria and tetanus. The fourth and fifth doses
- are boosters for diphtheria and tetanus immunization. [See *Clinical Studies (14.1, 14.2, 14.3).*]
- 14 DAPTACEL should be used as the fifth dose of the DTaP series in children who initially received
- 4 doses of Pentacel® [(Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed,
- 16 Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) vaccine, Sanofi
- 17 Pasteur Limited]. Pentacel and DAPTACEL contain the same pertussis antigens, manufactured by
- the same process, although Pentacel contains twice the amount of detoxified pertussis toxin (PT)
- and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL.
- 20 Data are not available on the safety and effectiveness of using mixed sequences of DAPTACEL
- 21 and DTaP vaccines from different manufacturers for successive doses of the DTaP vaccination
- series. DAPTACEL may be used to complete the immunization series in infants who have
- 23 received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of
- 24 DAPTACEL in such infants have not been fully demonstrated.
- 25 If a decision is made to withhold any recommended dose of pertussis vaccine, [see
- 26 Contraindications (4.2), (4.3) and Warnings and Precautions (5.2), Diphtheria and Tetanus
- 27 Toxoids Adsorbed For Pediatric Use (DT) should be administered.

2.2 Administration

28

- 29 Parenteral drug products should be inspected visually for particulate matter and discoloration
- prior to administration, whenever solution and container permit. If either of these conditions exist,
- 31 the product should not be administered.
- 32 After removing the "flip-off" cap, cleanse the vaccine vial stopper with a suitable germicide. Do
- 33 not remove either the rubber stopper or the metal seal holding it in place. Just before use, shake
- 34 the vial well, until a uniform, white, cloudy suspension results.
- Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL
- dose of DAPTACEL intramuscularly. Use a separate sterile needle and syringe for each injection.
- 37 Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient
- is not necessary unless the needle has been damaged or contaminated. In infants younger than 1
- 39 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of
- 40 injection. In older children, the deltoid muscle is usually large enough for injection. The vaccine
- should not be injected into the gluteal area or areas where there may be a major nerve trunk.
- 42 Do not administer this product intravenously or subcutaneously.
- DAPTACEL should not be combined through reconstitution or mixed with any other vaccine.

44 3 DOSAGE FORMS AND STRENGTHS

- DAPTACEL is a suspension for injection in 0.5 mL single dose vials. See *Description (11)* for a
- 46 complete listing of ingredients.

4 CONTRAINDICATIONS

48 4.1 Hypersensitivity

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- 49 A severe allergic reaction (eg, anaphylaxis) after a previous dose of DAPTACEL or any other
- tetanus toxoid, diphtheria toxoid, or pertussis-containing vaccine, or any other component of this
- vaccine is a contraindication to administration of DAPTACEL. [See *Description (11)*.] Because
- of uncertainty as to which component of the vaccine may be responsible, none of the components
- should be administered. Alternatively, such individuals may be referred to an allergist for
- evaluation if further immunizations are to be considered.

55 4.2 Encephalopathy

- Encephalopathy (eg., coma, decreased level of consciousness, prolonged seizures) within 7 days of
- a previous dose of a pertussis containing vaccine that is not attributable to another identifiable
- 58 cause is a contraindication to administration of any pertussis-containing vaccine, including
- 59 DAPTACEL.

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60 4.3 Progressive Neurologic Disorder

- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive
- encephalopathy is a contraindication to administration of any pertussis-containing vaccine,
- 63 including DAPTACEL. Pertussis vaccine should not be administered to individuals with such
- conditions until a treatment regimen has been established and the condition has stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

- 67 Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be
- available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.2 Adverse Reactions Following Prior Pertussis Vaccination

- 70 If any of the following events occur within the specified period after administration of a
- whole-cell pertussis vaccine or a vaccine containing an acellular pertussis component, the
- decision to administer DAPTACEL should be based on careful consideration of potential benefits
- 73 and possible risks. [See *Dosage and Administration (2.1)*.]
- Temperature of ≥40.5°C (105°F) within 48 hours, not attributable to another identifiable
- 75 cause.

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- Collapse or shock-like state (hypotonic-hyporesponsive episode (HHE)) within 48 hours.
- Persistent, inconsolable crying lasting ≥3 hours within 48 hours.
- Seizures with or without fever within 3 days.

79 5.3 Guillain-Barré Syndrome and Brachial Neuritis

- A review by the Institute of Medicine found evidence for a causal relation between tetanus toxoid
- and both brachial neuritis and Guillain-Barré syndrome. (1) If Guillain-Barré syndrome occurred
- within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré
- 83 syndrome may be increased following DAPTACEL.

84 5.4 Infants and Children with a History of Previous Seizures

- 85 For infants or children with a history of previous seizures, an appropriate antipyretic may be
- administered (in the dosage recommended in its prescribing information) at the time of
- vaccination with a vaccine containing an acellular pertussis component (including DAPTACEL)
- and for the following 24 hours, to reduce the possibility of post-vaccination fever.

89 5.5 Limitations of Vaccine Effectiveness

90 Vaccination with DAPTACEL may not protect all individuals.

91 **5.6 Altered Immunocompetence**

- 92 If DAPTACEL is administered to immunocompromised persons, including persons receiving
- 93 immunosuppressive therapy, the expected immune response may not be obtained. [See
- 94 *Immunosuppressive Treatments (7.2).*]

95 5.7 **Apnea in Premature Infants** 96 Apnea following intramuscular vaccination has been observed in some infants born prematurely. 97 The decision about when to administer an intramuscular vaccine, including DAPTACEL, to an 98 infant born prematurely should be based on consideration of the individual infant's medical status 99 and the potential benefits and possible risks of vaccination. 100 5.8 Syncope 101 Syncope (fainting) has been reported following vaccination with DAPTACEL. Procedures should 102 be in place to prevent falling injury and manage syncopal reactions. 6 ADVERSE REACTIONS 103 6.1 104 **Data from Clinical Studies** 105 Because clinical trials are conducted under widely varying conditions, adverse reaction rates 106 observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials 107 of another vaccine and may not reflect the rates observed in practice. The adverse reaction 108 information from clinical trials does, however, provide a basis for identifying the adverse events 109 that appear to be related to vaccine use and for approximating rates of those events. 110 Approximately 18,000 doses of DAPTACEL have been administered to infants and children in 9 111 clinical studies. Of these, 3 doses of DAPTACEL were administered to 4,998 children, 4 doses of 112 DAPTACEL were administered to 1,725 children, and 5 doses of DAPTACEL were administered 113 to 485 children. A total of 989 children received 1 dose of DAPTACEL following 4 prior doses of 114 Pentacel. 115 In a randomized, double-blinded pertussis vaccine efficacy trial, the Sweden I Efficacy Trial, 116 conducted in Sweden during 1992-1995, the safety of DAPTACEL was compared with DT and a 117 whole-cell pertussis DTP vaccine. A standard diary card was kept for 14 days after each dose and 118 follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were

made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months

after the last injection. There were fewer of the solicited common local and systemic reactions

following DAPTACEL than following the whole-cell pertussis DTP vaccine. As shown in Table

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- 1, the 2,587 infants who received DAPTACEL at 2, 4 and 6 months of age had similar rates of
- reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving
- whole-cell pertussis DTP.

125 Table 1: Percentage of Infants from Sweden I Efficacy Trial with Local or Systemic
126 Reactions within 24 Hours Post-Dose 1, 2 and 3 of DAPTACEL compared with
127 DT and Whole-Cell Pertussis DTP Vaccines

| | Dose 1 (2 MONTHS) | | | Dose 2 (4 MONTHS) | | | Dose 3 (6 MONTHS) | | |
|------------------------------|-----------------------|--------------------|---------------------|-----------------------|--------------------|---------------------|-----------------------|--------------------|---------------------|
| EVENT | DAPTACEL N = 2,587 | DT N = 2,574 | DTP N = 2,102 | DAPTACEL N = 2,563 | DT N = 2,555 | DTP N = 2,040 | DAPTACEL N = 2,549 | DT N = 2,538 | DTP N = 2,001 |
| Local | | | | | | | | | |
| Tenderness (Any) | 8.0* | 8.4 | 59.5 | 10.1* | 10.3 | 60.2 | 10.8* | 10.0 | 50.0 |
| Redness ≥2 cm | 0.3* | 0.3 | 6.0 | 1.0* | 0.8 | 5.1 | 3.7* | 2.4 | 6.4 |
| Swelling ≥2 cm | 0.9* | 0.7 | 10.6 | 1.6* | 2.0 | 10.0 | 6.3* [†] | 3.9 | 10.5 |
| Systemic | | | | | | | | | |
| Fever‡ ≥38°C (100.4°F) | 7.8* | 7.6 | 72.3 | 19.1* | 18.4 | 74.3 | 23.6* | 22.1 | 65.1 |
| Fretfulness§ | 32.3 | 33.0 | 82.1 | 39.6 | 39.8 | 85.4 | 35.9 | 37.7 | 73.0 |
| Anorexia | 11.2* | 10.3 | 39.2 | 9.1* | 8.1 | 25.6 | 8.4* | 7.7 | 17.5 |
| Drowsiness | 32.7* | 32.0 | 56.9 | 25.9* | 25.6 | 50.6 | 18.9* | 20.6 | 37.6 |
| Crying ≥1 hour | 1.7* | 1.6 | 11.8 | 2.5* | 2.7 | 9.3 | 1.2* | 1.0 | 3.3 |
| Vomiting | 6.9* | 6.3 | 9.5 | 5.2** | 5.8 | 7.4 | 4.3 | 5.2 | 5.5 |

- 128 DT: Swedish National Biologics Laboratories
- DTP: whole-cell pertussis DTP, Sanofi Pasteur Inc.
- N = Number of evaluable subjects
- * p<0.001: DAPTACEL versus whole-cell pertussis DTP
- † p<0.0001: DAPTACEL versus DT
- 133 ‡ Rectal temperature
- Statistical comparisons were not made for this variable
- ** p<0.003: DAPTACEL versus whole-cell pertussis DTP
- The incidence of serious and less common selected systemic events in the Sweden I Efficacy Trial
- is summarized in Table 2.

Table 2: Selected Systemic Events: Rates Per 1,000 Doses after Vaccination at 2, 4 and 6 Months of Age in Sweden I Efficacy Trial

| | | ose 1 ONTHS) | | | ose 2 ONTHS) | | Dose 3 (6 MONTHS) | | |
|---|-----------------------|--------------------|---------------------|-----------------------|--------------------|---------------------|-----------------------|--------------------|---------------------|
| EVENT | DAPTACEL N = 2,587 | DT N = 2,574 | DTP N = 2,102 | DAPTACEL N = 2,565 | DT N = 2,556 | DTP N = 2,040 | DAPTACEL N = 2,551 | DT N = 2,539 | DTP N = 2,002 |
| Rectal temperature ≥40°C (104°F) within 48 hours of vaccination | 0.39 | 0.78 | 3.33 | 0 | 0.78 | 3.43 | 0.39 | 1.18 | 6.99 |
| Hypotonic- hypo- responsive episode within 24 hours of vaccination | 0 | 0 | 1.9 | 0 | 0 | 0.49 | 0.39 | 0 | 0 |
| Persistent crying ≥3 hours within 24 hours of vaccination | 1.16 | 0 | 8.09 | 0.39 | 0.39 | 1.96 | 0 | 0 | 1.0 |
| Seizures within 72 hours of vaccination | 0 | 0.39 | 0 | 0 | 0.39 | 0.49 | 0 | 0.39 | 0 |

140 DT: Swedish National Biologics Laboratories

DTP: whole-cell pertussis DTP, Sanofi Pasteur Inc.

N = Number of evaluable subjects

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In the Sweden I Efficacy Trial, one case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL. Over the entire study period, 6 seizures were reported in the DAPTACEL group, 9 in the DT group and 3 in the whole-cell pertussis DTP group, for overall rates of 2.3, 3.5 and 1.4 per 1,000 vaccinees, respectively. One case of infantile spasms was reported in the DAPTACEL group. There were no instances of invasive bacterial infection or death.

| 151 | In a US study, children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of age. A |
|-----|---|
| 152 | total of 1,454 children received DAPTACEL and were included in the safety analyses. Of these, |
| 153 | 51.7% were female, 77.2% Caucasian, 6.3% Black, 6.5% Hispanic, 0.9% Asian and 9.1% other |
| 154 | races. The use of DAPTACEL as a fifth dose of DTaP vaccine was evaluated in 2 subsequent US |
| 155 | clinical studies. In one study, a total of 485 children received DAPTACEL at 4-6 years of age |
| 156 | following 4 prior doses of DAPTACEL in infancy (DAPTACEL-primed). In a separate study, a |
| 157 | total of 989 children received DAPTACEL at 4-6 years of age following 4 prior doses of Pentacel |
| 158 | in infancy (Pentacel-primed). The children included in these fifth dose studies were non-random |
| 159 | subsets of participants from previous DAPTACEL or Pentacel studies. The subsets were |
| 160 | representative of all children who received 4 doses of DAPTACEL or Pentacel in the earlier |
| 161 | studies with regard to frequencies of solicited local and systemic adverse events following the |
| 162 | fourth dose. |
| 163 | In the US 4-dose DAPTACEL study, at 2, 4, and 6 months of age, DAPTACEL was administered |
| 164 | concomitantly with Haemophilus influenzae type b (Hib) conjugate vaccine (tetanus toxoid |
| 165 | conjugate) (Sanofi Pasteur SA), inactivated poliovirus vaccine (IPV) (Sanofi Pasteur SA), and |
| 166 | 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.). Infants had received the |
| 167 | first dose of hepatitis B vaccine at 0 months of age. At 2 and 6 months of age, hepatitis B vaccine |
| 168 | (recombinant) (Merck & Co., Inc.) was also administered concomitantly with DAPTACEL. Based |
| 169 | on random assignment, the fourth dose of DAPTACEL was administered either alone; |
| 170 | concomitantly with Hib conjugate (tetanus toxoid conjugate) vaccine; or concomitantly with Hib |
| 171 | conjugate (tetanus toxoid conjugate) vaccine, 7-valent pneumococcal conjugate vaccine, measles, |
| 172 | mumps, rubella (MMR) vaccine (Merck & Co., Inc.), and varicella vaccine (Merck & Co., Inc.). |
| 173 | In the fifth dose studies, DAPTACEL was administered concomitantly with IPV (all |
| 174 | DAPTACEL-primed subjects and 47% of Pentacel-primed subjects) and MMR vaccine. |
| 175 | In the US studies, the occurrence of solicited local and systemic adverse events listed in Table 3 |
| 176 | was recorded daily by parents or guardians for Days 0-7 following vaccination. For Days 0 and 1 |
| 177 | following the first three doses of DAPTACEL, signs and symptoms of HHE also were solicited. |
| 178 | Periodic telephone calls were made to inquire about adverse events. Serious adverse events were |
| 179 | monitored during the three studies, through 6 months following the last dose of DAPTACEL. |

| 180 | The incidence and severity of selected solicited local and systemic adverse events that occurred |
|-----|--|
| 181 | within 3 days following each dose of DAPTACEL are shown in Table 3. The incidence of |
| 182 | redness, tenderness and swelling at the DAPTACEL injection site increased with the fourth and |
| 183 | fifth doses, with the highest rates reported after the fifth dose. The incidence of redness, |
| 184 | tenderness and swelling at the DAPTACEL injection site was similarly increased when |
| 185 | DAPTACEL was given as a fifth dose of DTaP vaccine in Pentacel-primed children. |

Table 3: Number (Percentage) of Children from US Studies with Selected Solicited Local and Systemic Adverse Events by Severity Occurring Between 0 to 3 Days after Each Dose of DAPTACEL

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| | Dose 1* | Dose 2* | Dose 3* | Dose 4* | Dos | se 5 |
|---|---------------|--------------------|---------------|--------------------|----------------------|----------------------|
| | | | | | DAPTACEL- primed* | Pentacel- primed* |
| | N = 1390-1406 | N = 1346-1360 % | N = 1301-1312 | N = 1118-1144 % | N = 473-481 | N = 936-981 % |
| Injection Site Reactions DAPTACEL injection | | | | | | |
| site) | | | | | | |
| Redness | 6.2 | 7.1 | 0.6 | 17.2 | 27.0 | 20.2 |
| >5 mm | 6.2 | 7.1 | 9.6 | 17.3 | 35.8 | 20.2 |
| 25 - 50 mm | 0.6 | 0.5 | 1.9 | 6.3 | 10.4 | 6.8 |
| >50 mm | 0.4 | 0.1 | 0.0 | 3.1 | 15.8 | 6.6 |
| Swelling | | | | | | |
| >5 mm | 4.0 | 4.0 | 6.5 | 11.7 | 23.9 | 12.0 |
| 25 - 50 mm | 1.2 | 0.6 | 1.0 | 3.2 | 5.8 | 4.1 |
| >50 mm | 0.4 | 0.1 | 0.1 | 1.6 | 7.7 | 2.9 |
| Tenderness† | | | | | | |
| Any | 48.8 | 38.2 | 40.9 | 49.5 | 61.5 | 50.0 |
| Moderate | 16.5 | 9.9 | 10.6 | 12.3 | 11.2 | 7.4 |
| Severe | 4.1 | 2.3 | 1.7 | 2.2 | 1.7 | 0.3 |
| | 7.1 | 2.3 | 1./ | 2.2 | 1./ | 0.5 |
| Increase in Arm | | | | | | |
| Circumference‡ | | | | | | |
| >5 mm | - | = | = | 30.1 | 38.3 | 28.6 |
| 20 - 40 mm | | | | 7.0 | 14.0 | 7.6 |
| >40 mm | | | | 0.4 | 1.5 | 1.2 |
| Interference with | | | | | | |
| Normal Activity of the | | | | | | |
| Arm§ | | | | | | |
| Any | - | - | - | - | 20.4 | 8.8 |
| Moderate | | | | | 5.6 | 1.7 |
| Severe | | | | | 0.4 | 0.0 |
| Systemic Reactions | | | | | | |
| | | | | | | |
| Fever** | 0.2 | 16.1 | 15.0 | 10.5 | (1 | 1.0 |
| ≥38.0°C | 9.3 | 16.1 | 15.8 | 10.5 | 6.1 | 4.6 |
| >38.5-39.5°C | 1.5 | 3.9 | 4.8 | 2.7 | 2.1 | 2.0 |
| >39.5°C | 0.1 | 0.4 | 0.3 | 0.7 | 0.2 | 0.2 |
| Decreased | | | | | | |
| Activity/Lethargy†† | | | | | | |
| Any | 51.1 | 37.4 | 33.2 | 25.3 | 21.0 | 12.6 |
| Moderate | 23.0 | 14.4 | 12.1 | 8.2 | 5.8 | 3.6 |
| Severe | 1.2 | 1.4 | 0.6 | 1.0 | 0.8 | 0.4 |
| Inconsolable Crying‡‡ | | - | | | 1 - | • |
| Any | 58.5 | 51.4 | 47.9 | 37.1 | 14.1 | 7.2 |
| Moderate | 14.2 | 12.6 | 10.8 | 7.7 | 3.5 | 1.9 |
| Severe | 2.2 | 3.4 | 1.4 | 1.5 | 0.4 | 0.3 |
| | | | | | | |

| | Dose 1* | Dose 2* | Dose 3* | Dose 4* | Do | se 5 |
|--------------------------|---------------|--------------------|---------------|--------------------|----------------------|----------------------|
| | | | | | DAPTACEL- primed* | Pentacel- primed* |
| | N = 1390-1406 | N = 1346-1360 % | N = 1301-1312 | N = 1118-1144 % | N = 473-481 | N = 936-981 % |
| Fussiness/Irritability§§ | | | | | | |
| Any | 75.8 | 70.7 | 67.1 | 54.4 | 34.9 | 22.9 |
| Moderate | 27.7 | 25.0 | 22.0 | 16.3 | 7.5 | 5.3 |
| Severe | 5.6 | 5.5 | 4.3 | 3.9 | 0.4 | 0.5 |

- * In one U.S. study, children received four doses of DAPTACEL. A non-random subset of these children received a fifth dose of DAPTACEL in a subsequent study. A non-random subset of children previously vaccinated with 4 doses of Pentacel in previous clinical studies received a dose of DAPTACEL at 4-6 years of age as the fifth dose of DTaP vaccine in another clinical study.
- † Doses 1-4 Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved. Dose 5 Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
- The circumference of the DAPTACEL-injected arm at the level of the axilla was monitored following the fourth and fifth doses only. Increase in arm circumference was calculated by subtracting the baseline circumference pre-vaccination (Day 0) from the circumference post-vaccination.
- Moderate: decreased use of arm, but did not require medical care or absenteeism; Severe: incapacitating, refusal to move arm, may have/or required medical care or absenteeism.
- For Doses 1-3, 53.7% of temperatures were measured rectally, 45.1% were measured axillary, 1.0% were measured orally, and 0.1% were measured by an unspecified route. For Dose 4, 35.7% of temperatures were measured rectally, 62.3% were measured axillary, 1.5% were measured orally, and 0.5% were measured by an unspecified route. For Dose 5 in DAPTACEL-primed children, 0.2% of temperatures were measured rectally, 11.3% were measured axillary, and 88.4% were measured orally. For Dose 5 in Pentacel-primed children, 0.2% of temperatures were measured rectally, 0.5% were measured tympanically, 17% were measured axillary, and 81.7% were measured orally. Fever is based upon actual temperatures recorded with no adjustments to the measurement for route.
- †† Dose 1-4 Moderate: interferes with and limits daily activity, less interactive; Severe: disabling (not interested in usual daily activity, subject cannot be coaxed to interact with caregiver).
 - Dose 5 Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
- Doses 1-4 Moderate: 1 to 3 hours inconsolable crying; Severe: >3 hours inconsolable crying.

 Dose 5 Moderate: interfered with activities, but did not require medical care or absenteeism;

 Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
- Doses 1-4 Moderate: Irritability for 1 to 3 hours; Severe: irritability for >3 hours.

 Dose 5 Moderate: interfered with activities, but did not require medical care or absenteeism;

 Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.

| 189 | In the US study in which children received 4 doses of DAPTACEL, of 1,454 subjects who |
|-----|--|
| 190 | received DAPTACEL, 5 (0.3%) subjects experienced a seizure within 60 days following any dose |
| 191 | of DAPTACEL. One seizure occurred within 7 days post-vaccination: an infant who experienced |
| 192 | an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures |
| 193 | occurred between 8 and 30 days post-vaccination. Of the seizures that occurred within 60 days |
| 194 | post-vaccination, 3 were associated with fever. In this study, there were no reported cases of HHE |
| 195 | following DAPTACEL. There was one death due to aspiration 222 days post-vaccination in a |
| 196 | subject with ependymoma. Within 30 days following any dose of DAPTACEL, 57 (3.9%) |
| 197 | subjects reported at least one serious adverse event. During this period, the most frequently |
| 198 | reported serious adverse event was bronchiolitis, reported in 28 (1.9%) subjects. Other serious |
| 199 | adverse events that occurred within 30 days following DAPTACEL include three cases of |
| 200 | pneumonia, two cases of meningitis and one case each of sepsis, pertussis (post-dose 1), |
| 201 | irritability and unresponsiveness. |
| 202 | In the US study in which DAPTACEL was administered as a fifth DTaP dose in DAPTACEL- |
| 203 | primed subjects, within 30 days following the fifth consecutive dose of DAPTACEL, 1 (0.2%) |
| 204 | subject reported 2 serious adverse events (bronchospasm and hypoxia). In the US study in which |
| 205 | DAPTACEL was administered as a fifth DTaP dose in Pentacel-primed subjects, within 30 days |
| 206 | following DAPTACEL, 4 (0.4%) subjects reported one or more serious adverse events (asthma |
| 207 | and pneumonia; idiopathic thrombocytopenic purpura; vomiting; cellulitis not at the injection |
| 208 | site). In these two studies, there were no reports of seizures within 30 days following DAPTACEI |
| 209 | in either the DAPTACEL-primed subjects or Pentacel-primed subjects. |
| 210 | In another study (Sweden II Efficacy Trial), 3 DTaP vaccines and a whole-cell pertussis DTP |
| 211 | vaccine, none of which are licensed in the US, were evaluated to assess relative safety and |
| 212 | efficacy. This study included HCPDT, a vaccine made of the same components as DAPTACEL |
| 213 | but containing twice the amount of detoxified PT and four times the amount of FHA (20 mcg |
| 214 | detoxified PT and 20 mcg FHA). HHE was observed following 29 (0.047%) of 61,220 doses of |
| 215 | HCPDT; 16 (0.026%) of 61,219 doses of an acellular pertussis vaccine made by another |
| 216 | manufacturer; and 34 (0.056%) of 60,792 doses of a whole-cell pertussis DTP vaccine. There |
| 217 | were 4 additional cases of HHE in other studies using HCPDT vaccine for an overall rate of |
| 218 | 33 (0.047%) in 69.525 doses. |

| 219 | In a randomized, parallel-group, US multi-center clinical trial conducted in children 4 through 6 |
|--|---|
| 220 | years of age, DAPTACEL was administered as follows: concomitantly with IPV (Sanofi Pasteur |
| 221 | SA) followed 30 days later by Menactra® [Meningococcal (Groups A, C, Y and W-135) |
| 222 | Polysaccharide Diphtheria Toxoid Conjugate vaccine, Sanofi Pasteur Inc.] [Group A]; |
| 223 | concomitantly with Menactra followed 30 days later by IPV [Group B]; or 30 days after |
| 224 | concomitant administration of Menactra and IPV [Group C]. Solicited injection site and systemic |
| 225 | reactions were recorded in a diary card for 7 consecutive days after each vaccination. For all study |
| 226 | groups, the most frequently reported solicited local reaction at the DAPTACEL injection site was |
| 227 | pain: 71.7%, 69.4% and 52.1% of subjects in Groups A, B and C, respectively. For all study |
| 228 | groups, the most frequently reported systemic reaction after DAPTACEL vaccination was |
| 229 | myalgia: 46.2%, 37.3% and 25.8% of subjects in Groups A, B and C, respectively. Fever >39.5°C |
| 230 | occurred at <1.0% in all groups. |
| 231 | |
| | |
| 232 | 6.2 Data from Post-Marketing Experience |
| 232 | 6.2 Data from Post-Marketing Experience |
| 232233 | 6.2 Data from Post-Marketing Experience The following adverse events have been spontaneously reported during the post-marketing use of |
| | |
| 233 | The following adverse events have been spontaneously reported during the post-marketing use of |
| 233 234 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a |
| 233234235 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or |
| 233 234 235 236 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. |
| 233 234 235 236 237 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on one or more of the following factors: |
| 233 234 235 236 237 238 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to DAPTACEL. |
| 233 234 235 236 237 238 239 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to DAPTACEL. • Blood and lymphatic disorders |
| 233 234 235 236 237 238 239 240 | The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to DAPTACEL. • Blood and lymphatic disorders Lymphadenopathy |

| 244 | Nausea, diarrhea |
|-----|--|
| 245 | General disorders and administration site conditions |
| 246 | Local reactions: injection site pain, injection site rash, injection site nodule, injection site |
| 247 | mass, extensive swelling of injected limb (including swelling that involves adjacent joints). |
| 248 | Infections and infestations |
| 249 | Injection site cellulitis, cellulitis, injection site abscess |
| 250 | • Immune system disorders |
| 251 | Hypersensitivity, allergic reaction, anaphylactic reaction (edema, face edema, swelling face, |
| 252 | pruritus, rash generalized) and other types of rash (erythematous, macular, maculo-papular) |
| 253 | Nervous system disorders |
| 254 | Convulsions: febrile convulsion, grand mal convulsion, partial seizures |
| 255 | HHE, hypotonia, somnolence, syncope |
| 256 | Psychiatric disorders |
| 257 | Screaming |
| 258 | |
| | |
| 259 | 7 DRUG INTERACTIONS |
| 260 | 7.1 Concomitant Administration with Other Vaccines |
| 261 | In clinical trials, DAPTACEL was administered concomitantly with one or more of the following |
| 262 | US licensed vaccines: Hib conjugate vaccine, IPV, hepatitis B vaccine, pneumococcal conjugate |
| 263 | vaccine, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid |
| 264 | Conjugate vaccine, MMR vaccine, and varicella vaccine. [See Adverse Reactions (6.1) and |
| 265 | Clinical Studies (14.4).] When DAPTACEL is given at the same time as another injectable |
| 266 | vaccine(s), the vaccines should be administered with different syringes and at different injection |
| 267 | sites. |
| 268 | In cases where DAPTACEL and Menactra are to be administered to children 4 through 6 years of |
| 269 | age, the two vaccines should be administered concomitantly or Menactra should be administered |
| 270 | prior to DAPTACEL. Administration of Menactra one month after DAPTACEL has been shown |
| 271 | to reduce meningococcal antibody responses to Menactra. [See Adverse Reactions (6.1) and |
| 272 | Clinical Studies (14.4).] |

7.2 273 **Immunosuppressive Treatments** 274 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic 275 drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune 276 response to DAPTACEL. 8 **USE IN SPECIFIC POPULATIONS** 277 278 8.1 **Pregnancy** 279 DAPTACEL is not approved for use in individuals 7 years of age and older. Human or animal 280 data are not available to assess vaccine-associated risks in pregnancy. 281 8.2 Lactation 282 DAPTACEL is not approved for use in individuals 7 years of age and older. Human or animal 283 data are not available to assess the impact of DAPTACEL on milk production, its presence in 284 breast milk, or its effects on the breastfed infant. **Pediatric Use** 285 8.4 286 DAPTACEL is not indicated for use in infants below 6 weeks of age or children 7 years of age or 287 older. Safety and effectiveness of DAPTACEL in these age groups have not been established.

11 DESCRIPTION 288 289 DAPTACEL is a sterile isotonic suspension of pertussis antigens and diphtheria and tetanus 290 toxoids adsorbed on aluminum phosphate, for intramuscular injection. 291 Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid and acellular pertussis 292 antigens [10 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg 293 pertactin (PRN), and 5 mcg fimbriae types 2 and 3 (FIM)]. 294 Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg of aluminum) as 295 the adjuvant, \leq 5 mcg residual formaldehyde, \leq 50 ng residual glutaraldehyde and 3.3 mg (0.6% 296 v/v) 2-phenoxyethanol (not as a preservative). 297 The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures 298 grown in Stainer-Scholte medium (2) modified by the addition of casamino acids and 299 dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant 300 culture medium. The FIM components are extracted and co-purified from the bacterial cells. The 301 pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and 302 chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde, and the 303 residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately 304 onto aluminum phosphate. 305 Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (3) After 306 purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde 307 and diafiltered. Clostridium tetani is grown in modified Mueller-Miller casamino acid medium 308 without beef heart infusion. (4) Tetanus toxin is detoxified with formaldehyde and purified by 309 ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually 310 adsorbed onto aluminum phosphate. 311 The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum 312 phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection.

313 Both diphtheria and tetanus toxoids induce at least 2 units of antitoxin per mL in the guinea pig 314 potency test. The potency of the acellular pertussis vaccine components is determined by the 315 antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by 316 enzyme-linked immunosorbent assay (ELISA). 12 CLINICAL PHARMACOLOGY 317 318 12.1 **Mechanism of Action** 319 **Diphtheria** 320 Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of C diphtheriae. 321 Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. 322 A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of 323 protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (5) Levels 324 of 1.0 IU/mL have been associated with long-term protection. (6) 325 Tetanus 326 Tetanus is an acute disease caused by an extremely potent neurotoxin produced by C tetani. 327 Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A 328 serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is 329 considered the minimum protective level. (5) (7) A tetanus antitoxin level ≥0.1 IU/mL as 330 measured by the ELISA used in clinical studies of DAPTACEL is considered protective. 331 **Pertussis** 332 Pertussis (whooping cough) is a respiratory disease caused by *B pertussis*. This Gram-negative 333 coccobacillus produces a variety of biologically active components, though their role in either the 334 pathogenesis of, or immunity to, pertussis has not been clearly defined.

13 NON-CLINICAL TOXICOLOGY 335 336 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 337 DAPTACEL has not been evaluated for carcinogenic or mutagenic potential or impairment of 338 fertility. **CLINICAL STUDIES** 14 339 340 14.1 **Diphtheria** 341 In a US study in which children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of 342 age, after the third dose, 100% (N = 1,099) achieved diphtheria antitoxin levels of ≥ 0.01 IU/mL 343 and 98.5% achieved diphtheria antitoxin levels of ≥0.10 IU/mL. Among a random subset of 344 children who received the fourth dose of DAPTACEL at 15-16 months of age, 96.5% (N = 659) 345 achieved diphtheria antitoxin levels of ≥ 1.0 IU/mL after the fourth dose. 346 14.2 Tetanus 347 In a US study in which children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of 348 age, after the third dose, 100% (N = 1,037) achieved tetanus antitoxin levels of ≥ 0.10 IU/mL. 349 Among a random subset of children who received the fourth dose of DAPTACEL at 15-16 350 months of age, 98.8% (N = 681) achieved tetanus antitoxin levels of ≥ 1.0 IU/mL after the fourth 351 dose. 352 14.3 Pertussis 353 A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in 354 Sweden during 1992-1995 (Sweden I Efficacy Trial) under the sponsorship of the National 355 Institute of Allergy and Infectious Diseases. A total of 9,829 infants received 1 of 4 vaccines: 356 DAPTACEL (N = 2,587); another investigational acellular pertussis vaccine (N = 2,566); whole-357 cell pertussis DTP vaccine (N = 2,102); or DT vaccine as placebo (Swedish National 358 Bacteriological Laboratory, N = 2,574). Infants were immunized at 2, 4 and 6 months of age. The 359 mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of 360 DAPTACEL against pertussis after 3 doses using the World Health Organization (WHO) case

| definition (\geq 21 consecutive days of paroxysmal cough with culture or serologic confirmation or |
|---|
| epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1 to 88.6). |
| The protective efficacy of DAPTACEL against mild pertussis (≥1 day of cough with laboratory |
| confirmation) was 77.9% (95% CI 72.6 to 82.2). Protection against pertussis by DAPTACEL was |
| sustained for the 2-year follow-up period. |
| In order to assess the antibody response to the pertussis antigens of DAPTACEL in the US |
| population, 2 lots of DAPTACEL, including the lot used in the Sweden I Efficacy Trial, were |
| administered to US infants in the US Bridging Study. In this study, antibody responses following |
| 3 doses of DAPTACEL given to US children at 2, 4 and 6 months of age were compared to those |
| from a subset of the infants enrolled in the Sweden I Efficacy Trial. Assays were performed in |
| parallel on the available sera from the US and Swedish infants. Antibody responses to all the |
| antigens were similar except for those to the PRN component. For both lots of DAPTACEL, the |
| geometric mean concentration (GMC) and percent response to PRN in US infants (Lot 006, N |
| = 107 ; Lot 009 , N = 108) were significantly lower after 3 doses of vaccine than in Swedish infants |
| (N=83). In separate US and Canadian studies in which children received DAPTACEL at 2, 4 and |
| 6 months of age, with a fourth dose at either 17-20 months (Canadian study) or 15-16 months |
| (random subset from US study) of age, antibody responses to each pertussis antigen following the |
| fourth dose (Canadian study $N = 275$; US study $N = 237-347$) were at least as high as those seen |
| in the Swedish infants after 3 doses. While a serologic correlate of protection for pertussis has not |
| been established, the antibody response to all antigens in North American infants after 4 doses of |
| DAPTACEL at 2, 4, 6 and 15-20 months of age was comparable to that achieved in Swedish |
| infants in whom efficacy was demonstrated after 3 doses of DAPTACEL at 2, 4 and 6 months of |
| age. |
| |

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14.4 Concomitantly Administered Vaccines 385 In the US Bridging study, DAPTACEL was given concomitantly with Hib conjugate vaccine 386 (Sanofi Pasteur SA) according to local practices. Anti-PRP immune response was evaluated in 387 261 infants who received 3 doses of Hib conjugate vaccine. One month after the third dose, 96.9% 388 achieved anti-PRP antibody levels of at least 0.15 mcg/mL and 82.7% achieved antibody levels of 389 at least 1.0 mcg/mL. 390 In the US study in which infants received DAPTACEL concomitantly with Hib conjugate (tetanus 391 toxoid conjugate) vaccine, IPV, 7-valent pneumococcal conjugate vaccine, and hepatitis B 392 vaccine [see Adverse Reactions (6.1)], at 7 months of age, 100.0% of subjects (N = 1,050-1,097) 393 had protective neutralizing antibody levels (>1:8 1/dil) for poliovirus types 1, 2 and 3; and 92.4% 394 (N = 998) achieved anti-hepatitis B surface antigen levels ≥ 10.0 mIU/mL. Although there is no 395 established serologic correlate of protection for any of the pneumococcal serotypes, at 7 months 396 of age 91.3%-98.9% (N = 1,027-1,029) achieved anti-pneumococcal polysaccharide levels ≥ 0.5 397 mcg/mL for serotypes 4, 9V, 14, 18C, 19F and 23F and 80.7% (N = 1,027) achieved an anti-398 pneumococcal polysaccharide level ≥0.5 mcg/mL for serotype 6B. The mumps seroresponse rate 399 was lower when DAPTACEL was administered concomitantly (86.6%; N = 307) vs. 400 non-concomitantly (90.1%; N = 312) with the first dose of MMR vaccine [upper limit of 90% 401 confidence interval for difference in rates (non-concomitant minus concomitant) >5%]. There was 402 no evidence for interference in the immune response to the measles, rubella, and varicella 403 antigens or to the fourth dose of the 7-valent pneumococcal conjugate vaccine with concomitant 404 administration of DAPTACEL. 405 In a randomized, parallel-group, US multi-center clinical trial conducted in children 4 through 6 406 years of age, DAPTACEL was administered as follows: concomitantly with IPV (Sanofi Pasteur 407 SA) followed 30 days later by Menactra [Group A]; concomitantly with Menactra followed 30 408 days later by IPV [Group B]; or 30 days after concomitant administration of Menactra and IPV 409 [Group C]. Sera were obtained approximately 30 days after each respective vaccination. When 410 DAPTACEL was administered concomitantly with Menactra [Group B], antibody responses to 411 PT, FHA and PRN (GMC), tetanus (% participants with antibody concentrations $\geq 1.0 \text{ IU/mL}$), 412 and diphtheria (%participants with antibody concentrations ≥1.0 IU/mL) were non-inferior to

| 413 | those observed when DAPTACEL (and IPV) were administered [Group A]. The anti-FIM GMCs |
|-----|---|
| 414 | were marginally lower when DAPTACEL and Menactra were administered concomitantly but the |
| 415 | clinical significance is unknown because there are no established serological correlates of |
| 416 | protection for pertussis. When DAPTACEL (and IPV) were administered 30 days prior to |
| 417 | Menactra [Group A], significantly lower serum-bactericidal assay-human complement (SBA-H) |
| 418 | GMTs to all 4 meningococcal serogroups were observed compared to when Menactra (and IPV) |
| 419 | were administered 30 days prior to DAPTACEL [Group C]. When DAPTACEL was administered |
| 420 | concomitantly with Menactra [Group B], SBA-H GMTs to meningococcal serogroups A, C, and |
| 421 | W-135 were non-inferior to those observed when Menactra (and IPV) were administered [Group |
| 422 | C]. The non-inferiority criterion was marginally missed for meningococcal serogroup Y. [See |
| 423 | Drug Interactions (7.1).] |

REFERENCES 15 424 425 426 1 Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence 427 bearing on causality. Washington D.C.: National Academy Press. 1994. p. 67-117. 428 2 Stainer DW, Scholte MJ. A simple chemically defined medium for the production of phase I 429 Bordetella pertussis. J Gen Microbiol 1970;63:211-20. 430 3 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings of an 431 informal consultation on the World Health Organization requirements for diphtheria, 432 tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda, 433 MD. DHHS 91-1174. 1991. p. 7-11. 434 4 Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J 435 Bacteriol 1954;67(3):271-7. 436 5 Department of Health and Human Services, Food and Drug Administration. Biological 437 products; bacterial vaccines and toxoids; implementation of efficacy review; proposed rule. 438 Federal Register 1985;50(240):51002-117. 439 6 Wharton M, et al. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th 440 ed. Philadelphia, PA: W. B. Saunders 2004 p. 211-28. 441 7 Wassilak SGF, et al. Tetanus Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th 442 ed. Philadelphia, PA: W. B. Saunders 2004 p. 745-81. 443 444

445 16 HOW SUPPLIED/STORAGE AND HANDLING

- The vial stopper for this product is not made with natural rubber latex.
- DAPTACEL is supplied in a single dose vial (NDC No. 49281-286-58):
- 448 in packages of 1 vial: NDC No. 49281-286-01;
- in packages of 5 vials: NDC No. 49281-286-05;
- 450 in packages of 10 vials: NDC No. 49281-286-10.
- DAPTACEL should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has
- been exposed to freezing should not be used. Do not use after expiration date shown on the label.

453 17 PATIENT COUNSELING INFORMATION

- 454 Inform the parent or guardian of the following:
- The potential benefits and risks of immunization with DAPTACEL.
- The common adverse reactions that have occurred following administration of DAPTACEL or
- other vaccines containing similar components.
- Other adverse reactions can occur. Call healthcare provider with any adverse reactions of
- 459 concern.
- 460 Provide the Vaccine Information Statements (VIS), which are required by the National Childhood
- Vaccine Injury Act of 1986.

| 462 | Manufactured by: |
|-----|--|
| 463 | Sanofi Pasteur Limited |
| 464 | Toronto Ontario Canada |
| 465 | Distributed by: |
| 466 | Sanofi Pasteur Inc. |
| 467 | Swiftwater PA 18370 USA |
| 468 | US Patents: 4500639, 4687738, 4784589, 4997915, 5444159, 5667787, 5877298. |
| 469 | DAPTACEL® is a registered trademark of Sanofi Pasteur Limited. |
| 470 | |
| 471 | R10-0916 USA |
| 472 | |
| | SANOFI PASTEUR 🗳 |
| 473 | |

EXHIBIT 238

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ActHIB safely and effectively. See full prescribing information for ActHIB.

ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] **Solution for Intramuscular Injection** Initial U.S. Approval: 1993

----- INDICATIONS AND USAGE -----

ActHIB is a vaccine indicated for the prevention of invasive disease caused by Haemophilus influenzae type b. ActHIB vaccine is approved for use as a four dose series in infants and children 2 months through 5 years of age (1)

----- DOSAGE AND ADMINISTRATION -----

For intramuscular administration only

Four-dose series (0.5 mL each) by intramuscular injection:

- A three-dose primary series administered at 2, 4, and 6 months of age. (2.1)
- A single booster dose administered at 15-18 months of age. (2.1)

- DOSAGE FORMS AND STRENGTHS

Solution for injection: lyophilized powder to be reconstituted in supplied 0.4% Sodium Chloride diluent. A single dose, after reconstitution is 0.5 mL (3)

----- CONTRAINDICATIONS -----

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any

Haemophilus influenzae type b or tetanus toxoid-containing vaccine or any component of ActHIB vaccine. (4)

----- WARNINGS AND PRECAUTIONS -----

If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the potential benefits and risks of giving ActHIB vaccine must be evaluated. (5.2)

---- ADVERSE REACTIONS ---

Following administration of ActHIB vaccine in children 2-20 months of age, rates of adverse reactions varied by dose number and age of recipients:

- The most frequent systemic reactions after any dose for children 2 months to 16 months of age were fussiness/irritability (75%), inconsolable crying (58%) and decreased activity/lethargy (51%). (6.1)
- In children 15-20 months of age tenderness (20%) was the most common local reaction following a single dose. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: Month 201X

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*Sections or subsections omitted from the full prescribing information are not

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

- 4 ActHIB® is a vaccine indicated for the prevention of invasive disease caused by *Haemophilus*
- 5 influenzae (H. influenzae) type b. ActHIB is approved for use in children 2 months through
- 6 5 years of age.

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2 DOSAGE AND ADMINISTRATION

9 For intramuscular use only

2.1 Immunization Series

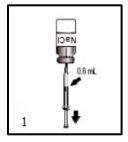
- 12 ActHIB vaccine is administered as a four-dose series (0.5 mL per dose) as:
- A primary three-dose series of a single dose at 2, 4, and 6 months of age.
- A single booster dose at 15 through 18 months of age.

2.2 Reconstitution

- 17 ActHIB vaccine is a solution for injection supplied as single-dose vials of lyophilized vaccine to
- be reconstituted only with the accompanying saline diluent (0.4% Sodium Chloride). To
- reconstitute ActHIB vaccine, withdraw 0.6 mL of saline diluent and inject into the vial of
- 20 lyophilized ActHIB vaccine. Agitate the vial to ensure complete reconstitution. The reconstituted
- 21 ActHIB vaccine will appear clear and colorless. Withdraw a 0.5-mL dose of the reconstituted
- vaccine and inject intramuscularly. After reconstitution, if ActHIB vaccine is not administered

- promptly store at 2° to 8°C (35° to 46°F) and administer within 24 hours. Stored vaccine should
- 2 be re-agitated prior to injection. Refer to Figures 1, 2, 3, and 4.
- 3 Instructions for Reconstitution of ActHIB Vaccine with Saline Diluent (0.4% Sodium

4 Chloride)



2 Activits



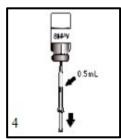


Figure 1. Disinfect the diluent vial stopper, inject the needle and withdraw 0.6 mL of 0.4% Sodium Chloride diluent as indicated.

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Figure 2. Cleanse the ActHIB vaccine stopper, insert the syringe needle into the vial, and inject the total volume of diluent.

Figure 3. Agitate vial thoroughly.

Figure 4. After reconstitution, withdraw 0.5 mL of reconstituted vaccine and administer intramuscularly.

2.3 Administration

- 8 Parenteral drug products should be inspected visually for particulate matter and/or discoloration
- 9 prior to administration, whenever solution and container permit. If either of these conditions exist,
- 10 the vaccine should not be administered.
- 12 ActHIB vaccine is administered as a single dose (0.5 mL) by intramuscular injection into the
- anterolateral aspect of the thigh or deltoid.
- 15 Do not administer this product intravenously, intradermally, or subcutaneously.

1 2 ActHIB vaccine should not be mixed in the same syringe with other parenteral products. 3 3 DOSAGE FORMS AND STRENGTHS 4 5 ActHIB vaccine is a solution for injection supplied as a single-dose vial of lyophilized powder to 6 be reconstituted with the supplied 0.4% Sodium Chloride diluent. A single dose, after reconstitution is 0.5 mL. 7 8 4 CONTRAINDICATIONS 9 10 4.1 **Hypersensitivity** 11 Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any *H. influenzae* type b or 12 tetanus toxoid-containing vaccine or any component of the vaccine is a contraindication to 13 administration of ActHIB vaccine [see DESCRIPTION (11)]. 14 5 WARNINGS AND PRECAUTIONS 15 16 **Management of Acute Allergic Reactions** 17 Epinephrine and other appropriate agents must be available should an acute anaphylactic reaction 18 occur. 19 20 5.2 Guillain-Barré Syndrome

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including ActHIB vaccine, should be based on careful consideration of the potential benefits and possible risks.

 5.3 Altered Immunocompetence
 In immunosuppressed persons, including those receiving immunosuppressive therapy, the expected antibody responses may not be obtained.
- 9 5.4 Limitations of Vaccine Effectiveness
- Vaccination with ActHIB vaccine may not protect 100% of individuals.
- 12 **5.5 Tetanus Immunization**

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- 13 Immunization with ActHIB vaccine does not substitute for routine tetanus immunization.
- 15 **5.6 Interference with Laboratory Tests**
- 16 Urine antigen detection may not have a diagnostic value in suspected disease due to *H influenzae*
- 17 type b within 1 to 2 weeks after receipt of a *H. influenzae* type b-containing vaccine, including
- 18 ActHIB [see DRUG INTERACTIONS (7.3)].

6 ADVERSE REACTIONS

2 6.1 Clinical Trials Experience

1

3 Because clinical trials are conducted under widely varying conditions, adverse reaction rates 4 observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials 5 of another vaccine and may not reflect the rates observed in practice. 6 7 More than 7,000 infants and young children (≤2 years of age) have received at least one dose of 8 ActHIB vaccine during US clinical trials. Of these, 1,064 subjects 12 to 24 months of age who 9 received ActHIB vaccine alone reported no serious or life threatening adverse reactions.(1) (2) 10 11 Adverse reactions associated with ActHIB vaccine generally subsided after 24 hours and did not 12 persist beyond 48 hours after immunization. 13 14 In a US trial, the safety of ActHIB vaccine was evaluated in 110 children 15 to 20 months of age. 15 All children received three doses of *Haemophilus influenzae* type b conjugate vaccine (ActHIB 16 vaccine or a previously licensed Haemophilus b conjugate vaccine) at approximately 2, 4, and 17 6 months of age. The incidence of selected solicited injection site and systemic adverse reactions 18 which occurred within 48 hours following the dose of ActHIB vaccine is shown in **Table 1**. 19 20

Table 1: Local and Systemic Reactions at 6, 24, and 48 Hours Following Immunization with

2 ActHIB Vaccine in Children 15 to 20 months old (2)

| Adverse Event | 6 Hrs. Post-dose | 24 Hrs. Post-dose | 48 Hrs. Post-dose |
|----------------------------------|------------------|-------------------|-------------------|
| Local (%) | N=110 | N=110 | N=110 |
| Tenderness | 20.0 | 8.2 | 0.9 |
| Erythema (>1") | 0.0 | 0.9 | 0.0 |
| Indurationa | 5.5 | 3.6 | 0.9 |
| Swelling | 3.6 | 1.8 | 0.0 |
| Systemic (%) | N=103-110 | N=105-110 | N=104-110 |
| Fever (>102.2°F) (>39.0°C) | 0 | 1.0 | 1.9 |
| Irritability | 27.3 | 20.9 | 12.7 |
| Drowsiness | 36.4 | 17.3 | 12.7 |
| Anorexia | 12.7 | 10.0 | 6.4 |
| Vomiting | 0.9 | 0.9 | 0.9 |
| Persistent cry | 0 | 0 | 0 |
| Unusual cry | 0 | 0 | 0 |

³ a Induration is defined as hardness with or without swelling.

- 5 In a US clinical trial (P3T06), 1,454 children were enrolled and received one dose of ActHIB
- 6 vaccine at 2 months of age and subsequent doses administered at 4 and 6 months of age
- 7 (concomitantly with DAPTACEL [a US-licensed diphtheria, tetanus and pertussis vaccine], IPOL
- 8 [a US-licensed inactivated poliovirus vaccine] and PCV7 [Pneumococcal conjugate vaccine,
- 9 7-valent]) vaccines at 2, 4, and 6 months of age and hepatitis B vaccine at 2 and 6 months of age).
- 10 At 15-16 months of age, 418 children received a 4th dose of ActHIB and DAPTACEL vaccines.
- 11 The most frequent systemic reactions following any dose (>50% of participants) were decreased
- 12 activity/lethargy, fussiness/irritability, and inconsolable crying.

Table 2: Number (Percentage) of Children with Selected Solicited Systemic Adverse

2 Reactions by Severity Occurring within 0-3 days After Vaccination in Study P3T06

| Systemic Reactions | DAPTA | CEL + IPOL + ActHI | DAPTACEL + ActHIB Vaccines | |
|--------------------------------|------------------------------|------------------------------|-------------------------------|--------------------------|
| Systemic Reactions | Dose 1 N=1,390-1,406 % | Dose 2 N=1,346-1,360 % | Dose 3 N=1,301-1,312 % | Dose 4 N=379-381 % |
| Fever ^{ab} | | | | |
| ≥38.0°C | 9.3 | 16.1 | 15.8 | 8.7 |
| >38.5°C | 1.6 | 4.3 | 5.1 | 3.2 |
| >39.5°C | 0.1 | 0.4 | 0.3 | 0.8 |
| Decreased | | | | |
| Activity/Lethargy ^c | | | | |
| Any | 51.1 | 37.4 | 33.2 | 24.1 |
| Moderate or Severe | 24.3 | 15.8 | 12.7 | 9.2 |
| Severe | 1.2 1.4 0.6 | | 0.3 | |
| Inconsolable Crying | | | | |
| Any | 58.5 | 51.4 | 47.9 | 36.2 |
| ≥1 hour | 16.4 | 16.0 | 12.2 | 10.5 |
| >3 hours | 2.2 | 3.4 | 1.4 | 1.8 |
| Fussiness/Irritability | | | | |
| Any | 75.8 | 70.7 | 67.1 | 53.8 |
| ≥1 hour | 33.3 | 30.5 | 26.2 | 19.4 |
| >3 hours | 5.6 | 5.5 | 4.3 | 4.5 |

Note. - Ages of study participants ranged from 1.3 to 19.5 months.

- other routes, or not recorded were 44.8%, 54.0%, 1.0%, and 0.1%, respectively. Following Dose 4, the proportion of
- temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 61.1%, 36.6%,
- 8 1.7%, and 0.5%, respectively.

6

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9 ° Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

In Study P3T06, within 30 days following any of Doses 1-3 of DAPTACEL + IPOL + ActHIB

- vaccines, 50 of 1,455 (3.4%) participants experienced a serious adverse event (SAE). One SAE of
- seizure with apnea occurring on the day of vaccination with the first dose of the three vaccines
- was determined by the investigators as possibly related. Within 30 days following Dose 4, four of

⁴ Fever is based upon actual temperatures recorded with no adjustments to the measurement route.

⁵ b Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or

- 1 418 (1.0%) participants who received DAPTACEL + ActHIB vaccines experienced a serious
- 2 adverse event. None was assessed by the investigators as related to the study of vaccines.

4 6.2 Postmarketing Experience

- 5 The following events have been spontaneously reported during the post-approval use of ActHIB
- 6 vaccine. Because these events are reported voluntarily from a population of uncertain size, it is
- 7 not always possible to reliably estimate their frequency or establish a causal relationship to
- 8 vaccine exposure.

3

- 9 Immune system disorders:
- Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- Nervous system disorders:
- 12 Convulsions

15

16

- General disorders and administration site conditions:
- Extensive limb swelling, peripheral edema, pruritus, rash (including generalized rash)

7 DRUG INTERACTIONS

17 7.1 Concomitant Administration with Other Vaccines

- In clinical trials, ActHIB vaccine was administered, at separate sites, concomitantly with one or
- more of the following vaccines: DTaP; Measles, Mumps and Rubella vaccine (MMR); Hepatitis
- 20 B vaccine; and Inactivated Poliovirus Vaccine (IPV). No impairment of the antibody response to
- 21 the individual antigens was demonstrated when ActHIB vaccine was given at the same time but
- separate sites with these vaccines.(2)

1 2 **Immunosuppressive Treatments** 3 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic 4 drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune 5 response to ActHIB vaccine [see WARNINGS AND PRECAUTIONS (5.3)]. 6 7 **Interference with Laboratory Tests** 8 Haemophilus b capsular polysaccharide derived from Haemophilus b Conjugate Vaccines has 9 been detected in the urine of some vaccinees. Urine antigen detection may not have a diagnostic 10 value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of a *H.* 11 influenzae type b-containing vaccine, including ActHIB [see WARNINGS AND PRECAUTIONS] 12 (5.6)7.(3) 13 **USE IN SPECIFIC POPULATIONS** 14 15 8.1 **Pregnancy** 16 ActHIB is not approved for use in individuals 6 years of age and older. No human or animal data 17 are available to assess vaccine-associated risks in pregnancy. 18

19

8.2 Lactation

- 1 ActHIB is not approved for use in individuals 6 years of age and older. Human or animal data are
- 2 not available to assess the impact of ActHIB on milk production, its presence in breast milk, or its
- 3 effects on the breastfed infant.

8.4 Pediatric Use

- 6 Safety and effectiveness of ActHIB have not been established in infants below the age of 6 weeks
- 7 and children and adolescents 6 years of age and older [see DOSAGE AND ADMINISTRATION]
- 8 (2.1)].

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11 DESCRIPTION

- 11 ActHIB vaccine is a sterile, lyophilized powder to be reconstituted with saline diluent (0.4%
- 12 Sodium Chloride) for intramuscular administration only. The vaccine consists of the *Haemophilus*
- influenzae type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), a high-molecular-
- weight polymer prepared from the *H. influenzae* type b strain 1482 grown in a semi-synthetic
- medium, covalently bound to tetanus toxoid. (4) The lyophilized ActHIB vaccine powder and
- saline diluent contain no preservative. The tetanus toxoid is prepared by extraction, ammonium
- sulfate purification, and formalin inactivation of the toxin from cultures of *Clostridium tetani*
- 18 (Harvard strain) grown in a modified Mueller and Miller medium. (5) The culture medium
- 19 contains milk-derived raw materials (casein derivatives). Further manufacturing process steps
- reduce residual formaldehyde to levels below 0.5 micrograms (mcg) per dose by calculation. The
- 21 toxoid is filter sterilized prior to the conjugation process. Potency of ActHIB vaccine is specified
- on each lot by limits on the content of PRP polysaccharide and protein in each dose and the

1 proportion of polysaccharide and protein in the vaccine that is characterized as high molecular 2 weight conjugate. 3 4 When ActHIB is reconstituted with saline diluent (0.4% Sodium Chloride), each 0.5-mL dose is 5 formulated to contain 10 mcg of purified capsular polysaccharide conjugated to 24 mcg of 6 inactivated tetanus toxoid and 8.5% of sucrose. 7 The vial stoppers for ActHIB vaccine and diluent are not made with natural rubber latex. 8 9 12 CLINICAL PHARMACOLOGY 10 12.1 Mechanism of Action 11 Haemophilus influenzae is a gram-negative coccobacillus. Most strains of H. influenzae that cause 12 invasive disease (e.g., sepsis and meningitis) are H. influenzae type b. 13 14 The response to ActHIB vaccine is typical of a T-dependent immune response to antigens. The 15 prominent isotype of anti-capsular PRP antibody induced by ActHIB vaccine is IgG. (6) A 16 booster response for IgG has been demonstrated in children 12 months of age or older who 17 previously received two or three doses of ActHIB vaccine. Bactericidal activity against H. 18 influenzae type b was demonstrated in serum after immunization and correlated with the anti-PRP 19 antibody response induced by ActHIB vaccine. (1) 20 21 Antibody titers to H. influenzae capsular polysaccharide (anti-PRP) of >1.0 mcg/mL following 22 vaccination with unconjugated PRP vaccine correlated with long-term protection against invasive 23 H. influenzae type b disease in children older than 24 months of age. (7) Although the relevance

- of this threshold to clinical protection after immunization with conjugate vaccines is not known,
- 2 particularly in light of the induced, immunologic memory, this level continues to be considered as
- 3 indicative of long-term protection. (8) In clinical studies, ActHIB vaccine induced, on average,
- 4 anti-PRP levels \geq 1.0 mcg/mL in 90% of infants after the primary series (2, 4, and 6 months) and
- 5 in more than 98% of infants following a booster dose given at 15 to 19 months of age. (1)

7 13 NON-CLINICAL TOXICOLOGY

- 8 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 9 ActHIB vaccine has not been evaluated for its carcinogenic or mutagenic potential or impairment
- of male fertility.

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12 14 CLINICAL STUDIES

- 13 14.1 Immunogenicity of ActHIB Vaccine in Children 2, 4, and 6 Months of Age
- 14 Two clinical trials supported by the National Institutes of Health (NIH) have compared the
- anti-PRP antibody responses to three *Haemophilus influenzae* type b conjugate vaccines in
- racially mixed populations of children. These studies were done in Tennessee (9) (**Table 3**) and in
- 17 Minnesota, Missouri, and Texas (10) (**Table 4**) in infants immunized with ActHIB vaccine and
- other *Haemophilus influenzae* type b conjugate vaccines at 2, 4, and 6 months of age. All
- 19 Haemophilus influenzae type b conjugate vaccines were administered concomitantly with OPV
- and whole-cell DTP vaccines at separate sites. Neither OPV nor whole-cell DTP vaccines are
- 21 licensed or distributed in the US currently.

1 Table 3: Anti-PRP Antibody Responses Following a Two or Three Dose Series of a

2 Haemophilus influenzae type b Vaccine at 2, 4, and 6 Months of Age – Tennessee (9)

| | | Geometric | Post Third Immunization | | |
|---|----------------|-------------------------------|----------------------------|---|------------------|
| Vaccine | N ^a | Immunization Immunization Imm | | Post Third Immunization at 7 months | % ≥1.0 mcg/mL |
| PRP-T ^b (ActHIB vaccine) | 65 | 0.10 | 0.30 | 3.64 | 83% |
| PRP-OMP ^c (PedvaxHIB [®]) | 64 | 0.11 | 0.84 | N/A | 50% ^d |
| HbOC ^e (HibTITER [®]) | 61 | 0.07 | 0.13 | 3.08 | 75% |

³ a N = Number of children

9 Table 4: Anti-PRP Antibody Responses Following a Two or Three Dose Series of a

10 Haemophilus influenzae type b Vaccine at 2, 4, and 6 Months of Age - Minnesota, Missouri,

11 **and Texas** (10)

| | Nia | Geometric | Mean Concentrat (mcg/mL) | tion (GMC) | Post Third ^b Immunization | |
|-------------------------------------|----------------|-------------------------------------|--|--|---|--|
| Vaccine | N ^a | Pre- Immunization at 2 months | Post Second Immunization at 6 months | Post Third ^b Immunization at 7 months | % ≥1.0 mcg/mL | |
| PRP-T ^c (ActHIB vaccine) | 142 | 0.25 | 1.25 | 6.37 | 97% | |
| PRP-OMP ^d (PedvaxHIB) | 149 | 0.18 | 4.00 | N/A | 85% ^e | |
| HbOC ^f (HibTITER) | 167 | 0.17 | 0.45 | 6.31 | 90% | |

¹² a N = Number of children

⁴ b Haemophilus influenzae type b Conjugate Vaccine (Tetanus Toxoid Conjugate)

⁶ d Seroconversion after the recommended 2-dose primary immunization series is shown

^{7 •} Haemophilus influenzae type b Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein Conjugate)

⁸ N/A = Not applicable in this comparison trial although third dose data have been published

¹³ b Sera were obtained after the third dose from 86 and 110 infants, in PRP-T and HbOC vaccine groups, respectively

¹⁵ d Haemophilus influenzae type b Conjugate Vaccine (Meningococcal Protein Conjugate)

¹⁶ e Seroconversion after the recommended 2-dose primary immunization series is shown

- 1 f Haemophilus influenzae type b Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein Conjugate)
- N/A = Not applicable in this comparison trial although third dose data have been published (10)
- 4 Native American populations have had high rates of *H. influenzae* type b disease and have been
- 5 observed to have low immune responses to *Haemophilus influenzae* type b conjugate vaccines. In
- 6 a clinical study enrolling Alaskan Native Americans, following the administration of a three-dose
- 7 series of ActHIB vaccine at 6 weeks, 4 months, and 6 months of age, 75% of subjects achieved an
- 8 anti-PRP antibody titer of \geq 1.0 mcg/mL at 7 months of age (1 month after the last vaccination).
- 9 (11)

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14.2 Immunogenicity of ActHIB Vaccine in Children 12 to 24 Months of Age

- 12 In four separate studies, children 12 to 24 months of age who had not previously received
- 13 Haemophilus influenzae type b conjugate vaccination were immunized with a single dose of
- 14 ActHIB vaccine (**Table 5**). Geometric Mean Concentration (GMC) of anti-PRP antibody
- responses were 5.12 mcg/mL (90% responding with ≥1.0 mcg/mL) for children 12 to 15 months
- of age and 4.4 mcg/mL (82% responding with ≥1.0 mcg/mL) for children 17 to 24 months of age.
- 17 (2)

18

Table 5: Anti-PRP Antibody Responses in 12- to 24-month-old Children Immunized with a

19 Single Dose of ActHIB

| Age Group | Na | | n Concentration mcg/mL) | % Subjects With ≥1.0 mcg/mL | |
|-----------------|-----|----------------------|--|--------------------------------|------------------------------------|
| Age Group | 1 | Pre- Immunization | Post- Pre- Immunization ^b Immuniza | | Post- Immunization ^b |
| 12 to 15 months | 256 | 0.06 | 5.12 | 1.6 | 90.2 |
| 17 to 24 months | 81 | 0.10 | 4.40 | 3.7 | 81.5 |

1 a N = Number of children

- 2 b Post immunization responses measured at approximately 1 month after vaccination 3
- 4 ActHIB vaccine has been found to be immunogenic in children with sickle cell anemia, a
- 5 condition that may cause increased susceptibility to *Haemophilus influenzae* type b disease.
- 6 Following two doses of ActHIB vaccine given at two-month intervals, 89% of these children
- 7 (mean age 11 months) had anti-PRP antibody titers of \geq 1.0 mcg/mL. This is comparable to
- 8 anti-PRP antibody levels demonstrated in children without sickle-cell anemia of similar age
- 9 following two doses of ActHIB vaccine. (12)

15 REFERENCES

1

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16 HOW SUPPLIED/STORAGE AND HANDLING

2 16.1 How Supplied

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- 3 Single-dose, lyophilized vaccine vial (NDC 49281-547-58) packaged with single-dose diluent vial
- 4 (NDC 49281-546-58). Supplied as package of 5 vials each (NDC 49281-545-03).
- 6 The vial stoppers for ActHIB vaccine and diluent are not made with natural rubber latex.

8 16.2 Storage and Handling

- 9 Store lyophilized ActHIB vaccine packaged with saline diluent (0.4% Sodium Chloride) at 2° to
- 10 8°C (35° to 46°F). DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

- 13 Vaccine Information Statements are required by the National Childhood Vaccine Injury Act of
- 14 1986 to be given prior to immunization to the patient, parent, or guardian.
- 16 Inform the patients, parents, or guardians about the potential benefits and risks of the vaccine and
- importance of completing the immunization series unless a contraindication to further
- 18 immunization exists. In addition to this, parents and guardians must be informed about the
- 19 potential for adverse reactions that have been temporarily associated with the administration of
- 20 ActHIB vaccine or other vaccines containing similar ingredients. Prior to administration of
- 21 ActHIB vaccine, healthcare providers should ask parents or guardians about the recent health
- status of the infant or child to be immunized. As part of the child's immunization record, the date,

| Vaccine recipients and guardians must report any adverse reactions upon administration of the vaccine to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS). |
|--|
| |
| (VAERS). |
| |
| |
| |
| ActHIB, DAPTACEL and IPOL are registered trademark of Sanofi Pasteur Inc. PedvaxHIB® is a registered trademark of Merck & Co., Inc. HibTITER® is a registered trademark of Nuron Biotech. |
| Product information |
| as of Month 201X. |
| |
| Manufactured by: |
| Sanofi Pasteur SA |
| Marcy L'Etoile France |
| |
| Distributed by: |
| Sanofi Pasteur Inc. |
| Swiftwater PA 18370 USA |
| |
| |
| 7274 |
| |





Summary for Basis of Approval

Reference Number: 90-0689

Drug Licensed Name:
Haemophilus b Conjugate Vaccine
(Tetanus Toxoid Conjugate)

Manufacturer:

Drug Trade Name:

Pasteur Merieux Serums & Vaccins, S.A.

ActHIB TM

Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), ActHIB™, is composed of the purified capsular polysaccharide isolated from *Haemophilus influenzae* type b covalently attached to tetanus toxoid prepared from the inactivated toxin of *Clostridium tetani*.

I. INDICATIONS AND USAGE

ActHIB™ is indicated for the active immunization of infants and children 2 months through of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b.

Levels of antibody associated with protection may not be achieved earlier than two weeks following the last recommended dose.

As with any vaccine, vaccination with ActHIB™ may not protect 100% of susceptible individuals.

II. DOSAGE AND ADMINISTRATION:

The vaccine is a sterile, lyophilized powder which is to be reconstituted just before use with the supplied saline diluent (0.4% sodium chloride). Each 0.5 mL dose of ActHIB is formulated to contain 10 µg of purified capsular polysaccharide conjugated to approximately 24 µg of tetanus toxoid. The vaccine also contains 8.5% sucrose. The vaccine and diluent contain no preservatives. The vaccine when reconstituted is colorless and should be injected intramuscularly in the outer aspect of the vastus lateralis (mid thigh) or deltoid. The vaccine should not be injected into the gluteal area or areas where there may be a nerve tract. In the event of ActHIB may be given in the lateral aspect of the thigh.

Infants between 2 and 6 months of age should receive three 0.5 mL doses at 6 to 8 week intervals, followed by a booster at 15 to 18 months of age. Infants 7 to 11 months of age who have not been previously immunized should receive two 0.5 mL doses at 6 to 8 week intervals, followed by a booster dose at 15 to 18 months of age. Children 12 to 14 months of age who have not been previously immunized should receive one 0.5 mL dose, followed by a booster at 15 to 18 months of age, but not less than 2 months

after the previous dose. Children 15 to months of age who have not been previously immunized should receive a single 0.5 mL dose. ActHIB is packaged in single dose vials with a 0.6 mL syringe containing 0.4% sodium chloride diluent.

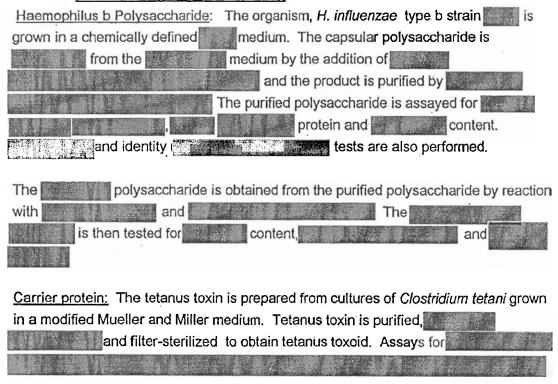
The recommended immunization schedule is summarized as follows:

| Age at Fin Dose (mo | 5007 | Booster |
|------------------------|-----------------------------|-------------------------|
| 2 to 6 | 3 Doses, 6 to 8 weeks apart | 1 Dose, 15 to 18 months |
| 7 to 11 | 2 Doses, 6 to 8 weeks apart | 1 Dose, 15 to 18 months |
| 12 to 14 | 1 Dose | 1 Dose, 15 to 18 months |
| 15 to 🄼 | 1 Dose | None |

The current recommendation of the Advisory Committee on Immunization Practices (ACIP) is for routine immunization of all children with Haemophilus b conjugate vaccine beginning at 2 months of age.

III. MANUFACTURING AND CONTROLS

A. Manufacturing and Control testing:



| percentage of and are performed. |
|--|
| Conjugation and purification: Tetanus toxoid and the polysaccharide are conjugated using to eliminate and conjugate. The bulk is sterilized by filtration. Assays are performed for and content, The potency test for this vaccine is a combination of two physical-chemical assays; percentage of HMWC and the protein to polysaccharide ratio. |
| Final vaccine: The final bulk vaccine is obtained from the concentrated bulk by in physical product in physical product is tested for identity, polysaccharide content, general safety, sterility, pyrogenicity, physical moisture, sucrose, percentage of HMWC, and shown in Table 1. |
| The manufacturer submitted three lots of vaccine, S2440, S2441 and S2468, for demonstration of manufacturing consistency as well as two later lots for release testing, H1025 and H0990. These lots met the specifications shown in Table 1. |
| B. Stability studies: The recommended storage temperature of the lyophilized vaccine and syringe containing diluent is +2° to +8° C (35° - 46° F). Stability of the vaccine was monitored by the evaluation of and Following storage of the vaccine at the recommended temperature range for nonths (three vaccine lots) and at higher temperatures, the product was shown to be stable. Based on results from these stability studies, the dating period is months at +2 to +8° C from the date of initiation of the final container potency tests (% HMWC and polysaccharide:protein ratio). Pasteur Merieux serums & Vaccins has made a commitment to an ongoing stability program. |

C. Validation:

The major equipment used in the manufacture and filling of the vaccine have been validated. In addition, appropriate specifications have been established for monitoring environmental conditions for each critical work area of the manufacturing facilities located in page 1. In ear Lyon, France.

D. <u>Labeling</u>: The package insert is in compliance with the appropriate sections, 610.60, 610.61, 610.62, 201.56, and 201.57, of 21 CFR and contains statements concerning use, contraindications, warnings, immunogenicity, experience, precautions, adverse reactions, dosage and administration, how supplied, and information on storage of the vaccine.

The primary label used on the vials of HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) states the following: the proper name and the trade name, HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) ActHIBTM; a statement referring to the package insert for dosage information; storage statements, DO NOT FREEZE. Store at 2° - 8°C (35° - 46°F); a caution stating to SHAKE WELL after reconstitution; space for adding lot number and expiration date at the time of packaging; the NDC number; Mfd. by: PASTEUR MERIEUX Serums & Vaccins S.A., Lyon, France, US. Lic. No. 384.

The primary label used on the vial of DILUENT FOR HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) states the following: contents of vial, 0.6 mL; contains (0.4% Sodium Chloride); space for adding a lot number and the expiration date at the time of labeling vials; Mfd. by PASTEUR MERIEUX Serums & Vaccins S.A., Lyon, France

The label on the unit carton for HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) states the following: the proper name and the trade name, HAEMOPHILUS b CONJUGATE VACCINE (Tetanus Toxoid Conjugate) ActHIBTM; contents of vials (1 dose); storage conditions, Store between 2° - 8°C (35° - 46° F); the caution statement concerning the federal dispensing law; a caution to SHAKE WELL after reconstitution; a statement referring to the package insert for indications and directions; a space for adding lot number and expiration date at the time of packaging; the NDC number; Mfd. by PASTEUR MERIEUX Serums & Vaccins S.A.,

Lyon, France, US. License No. 384. and distributed by Connaught Laboratories, Inc., Swiftwater, PA.

E. Establishment Inspection:

The facilities were inspected by the FDA on two separate occasions. The first preliminary inspection was done in June, 1991. The most recent pre-license inspection was on February 5-7, 1992. The facilities, manufacturing protocols, quality control laboratory, storage conditions, record keeping, and other aspects of conjugate manufacturing were considered to be satisfactory and in compliance with applicable regulatory requirements.

F. Environmental Assessment

Production of this product occurs entirely in France. Substances toxic to the environment are not released into the environment. Environmental assessment was filed, reviewed and a Finding of No Significant Impact was prepared for this product approval for Pasteur Merieux Serums et Vaccins. The company has stated that they are in compliance with all state, local or governmental requirements of the country in which production occurs.

IV. PHARMACOLOGY:

The manufacturer's labeling is adequate with respect to pharmacology. For additional information see the clinical pharmacology section of the attached package insert.

V. MEDICAL

A. General information:

For many years *H. influenzae* type b (Haemophilus b) has been the leading cause of invasive bacterial diseases, such as meningitis, septicemia and epiglottitis, in young children in the United States. Ninety-five percent of invasive Haemophilus b disease among children <5 years of age is caused by organisms with the type b polysaccharide capsule. Before effective vaccines were introduced, it was estimated that 1/200 children developed invasive Haemophilus b disease by 5 years of age. Sixty percent of these children had meningitis, with a 3% to 6% mortality rate. Permanent sequelae, ranging from mild hearing loss to mental retardation, affects 20% to 30% of survivors of Haemophilus b meningitis. Approximately two-thirds of all cases of invasive

Haemophilus b disease occur in infants and children <15 months of age, a group for which a vaccine was not available until 1990.^{1,2}

It has been shown by a number of investigators that the *H. influenzae* type b capsule is a major virulence factor. Antibodies to the capsular polysaccharide are bactericidal and opsonize the bacteria for phagocytic killing. Studies in the United States showed that the peak incidence of Haemophilus b disease occurs in children between 6 and 12 months of age, a time period in which the lowest antibody levels to the organism are found. In a field trial performed in Finland in 1974, the presence of antibodies induced by an Haemophilus b polysaccharide vaccine was shown to correlate with protection. Thus protection against Haemophilus b disease is correlated with the presence of antibody to the Haemophilus b polysaccharide.

An anti-PRP antibody titer ≥1.0 µg/mL following vaccination with unconjugated PRP vaccine was associated with long-term protection against invasive Haemophilus b disease. Although the relevance of this antibody threshold to clinical protection after immunization with a conjugate vaccine is not known, this level continues to be considered as indicative of long-term protection.

The incidence of invasive Haemophilus b disease is higher in Native Americans, Eskimos, children of lower socioeconomic status and those with asplenia, sickle cell disease, Hodgkin's disease, or immunodeficiency syndromes. Studies also have suggested that the risk of acquiring primary invasive Haemophilus b disease under 5 years of age appears to be higher for children attending day-care facilities.

The potential for person-to-person transmission of the Haemophilus b organism among susceptible individuals has been recognized. Studies of secondary spread of disease in household contacts of index patients have shown a substantially increased risk among exposed household members under 4 years of age.

The characteristics of an immune response depend on the type of cells producing the response and the antigens stimulating the response. Proteins induce B lymphocytes to produce antibody aided by thymus derived lymphocytes called T helper (TH) cells. Such antigens are called thymus-dependent or TD antigens. These antigens induce long lasting responses in young infants that prime for a booster type response on reexposure to the antigen. In contrast, polysaccharides stimulate B cells without TH

cell help, producing a response of both IgG and IgM antibodies that does not prime for a booster type response. These antigens are called thymus-independent or TI antigens. TI antigens are poorly immunogenic at best in young infants. Chemical linkage of the Haemophilus b polysaccharide or smaller oligosaccharides to a protein carrier such as tetanus toxoid apparently converts the TI saccharide to a TD antigen. This results in an enhanced antibody response, especially in infants, to the polysaccharide that is long-lasting, and is predominantly of the IgG isotype. The conjugate importantly primes for an anamnestic response on reexposure to the polysaccharide.

B. Brief description of clinical studies:

Overview: ActHIB™ has been administered to more than 200,000 infants worldwide during the program of clinical trials and over 500,000 infants in France following approval in that country. Few serious adverse reactions have been reported and, when given with DTP vaccine, the adverse experience profile is not different from that ordinarily seen when DTP is administered alone. Immunogenicity has been evaluated in more than 1,500 infants. After the primary three dose immunization series, ActHIB™ induces PRP antibody levels ≥1.0 µg/mL in approximately 90% of infants as measured by

Safety: Using the US immunization schedule at 2, 4, and 6 months of age and route of immunization, ActHIB™ has been evaluated for safety in over 7,400 children with in excess of 20,000 doses. Numbers of studies and age groups involved are summarized in Table 2. Most children under 12 months of age also received DTP and oral polio vaccines at the same visit. In a multicenter (GA, MS, OH, PA, UT) study 365 infants were followed for 72 hours after IM administration of ActHIB™ and DTP at separate sites. Data were collected after 6, 24, 48 and 72 hours and the reaction rates at 24 hours are shown in Table 3 (see also package insert Table 5). The rates of reactions were not different from those expected following administration of DTP alone. All reaction rates declined with time and by 72 hours most had resolved. In other studies approximately 1,450 doses of ActHIB™ were administered to 12 to 24 month-old children without any serious adverse events.

During an efficacy trial initiated in Southern California, 4,300 children received ActHIB™ and DTP at the same time in separate legs at approximately 2, 4 and 6 months of age. Of these, approximately 3,000 children were followed for 30 days for

both common and less common adverse reactions temporally associated with vaccine administration. A similar number of children received Hepatitis B vaccine in place of ActHIB™. The rates of adverse reactions were not significantly different for both groups. Less common events occurring within 30 days of immunization were monitored. After 13,000 doses of ActHIB™, 5 SIDS and 5 febrile seizures were seen in the ActHIB group, compared to 4 SIDS and 2 febrile seizures in the Hepatitis B group.

Additional safety data with ActHIB™ are available from the efficacy studies conducted in North Carolina (820 infants), in Oxford, England (26,600 infants, see reference 6), and in Finland (107,000 infants). In each of these studies the vaccine was well tolerated and no serious adverse reactions were reported.

Efficacy: Efficacy of ActHIB™ was evaluated based upon fulfillment of a series of immunological surrogates (described below). Approval of this vaccine was based primarily upon the immunological surrogates, because (1) two other Haemophilus b conjugate vaccines were approved for routine use infants in 1990, (2) the English trial did not use the US immunization schedule, and (3) because once an effective vaccine was approved in the US it becomes very difficult to conduct an acceptable controlled clinical trial to demonstrate efficacy of another vaccine for the same indication. The surrogate data are supported by a published report of efficacy in a field trial in England using a different immunization schedule than that recommended in the US.

Approval of the first Haemophilus b conjugate vaccine for use in infants in October, 1990, resulted in termination of two ongoing efficacy trials with ActHIB™ in approximately 12,000 subjects, half of whom received ActHIB™. It can be noted that at the time the studies were terminated no cases of Haemophilus b disease had occurred in subjects receiving the full three dose immunization series.

Some immunologic surrogates of an effective Haemophilus b conjugate vaccine are presented in Table 4. Studies of four different Haemophilus b conjugate vaccines have shown a number of common features that clearly differentiate the immune responses to conjugate vaccines from those to the unconjugated Haemophilus b polysaccharide. These include induction of antibodies in infants at an age when they do not respond to the free polysaccharide, induction of higher levels of Igamar relative to Igamar and priming of infants for a booster response to the native polysaccharide. However, conjugate vaccines differ from one another in the magnitude and duration of

the initial response after the recommended 2 or 3 dose immunization series. Protection against Haemophilus b disease is associated with opsonic and bactericidal antibodies directed against the capsular polysaccharide. It is likely that opsonic activity alone is sufficient because individuals with deficiencies in the late complement components appear not to be at increased risk of Haemophilus b disease, as they are for neisserial disease. Bactericidal and opsonic antibody levels to *H. influenzae* type b have been shown to correlate with one another. It was the opinion of the FDA Vaccines and Related Biological Products Advisory Committee in September 1991, that immunological criteria, as shown in Table 4, could be used as the basis for demonstrating clinical efficacy of a new Haemophilus b conjugate vaccine. This was confirmed again by the Committee a year later. These immunological surrogates were therefore used to demonstrate immunological equivalence between ActHIB and the two licensed Haemophilus b conjugate vaccines approved for administration to infants.

Immune surrogates for efficacy: It was important to determine whether ActHIB™ induced similar amounts of anti-Haemophilus b polysaccharide antibody and seroconversion rates to 1 ug/mL, compared to the other licensed vaccines. The immunogenicity of HibTITER®, PedVaxHib™, and ActHIB™ was compared in a randomized trial in 458 US. infants. All sera were blindly assayed at the Pediatric Division of Infectious Diseases,

Results show that 97% of ActHIB recipients had a PRP antibody concentration ≥1.0 μg/mL after the third dose, with a geometric mean titer of 6.37μg/mL (see Figure 1). By comparison, the values for HibTITER®, and PedVaxHib™ after the primary immunization series were 90% (6.31 ug/mL) and 85% (4.00 ug/mL) respectively. The antibody concentrations after the final dose of the primary series were not significantly different among the three groups.

A randomized comparative trial at Vanderbilt University School of Medicine (TN) compared the immunogenicity of two Haemophilus b conjugate vaccines (HibTITER[®], and PedVaxHib™) to ActHIB™, given at 2, 4 and 6 months concomitantly with DTP vaccine. All sera were blindly assayed at Vanderbilt University Pediatric Infectious Disease Laboratory. Results showed that 83% of ActHIB™ recipients had a PRP antibody concentration ≥1.0 µg/mL after the third dose, with a geometric mean titer of 3.64 µg/mL (see Figure 1). The comparable values for HibTITER[®], and PedVaxHib™ were 75% (3.08 µg/mL)

and 55% (1.14 ug/mL) respectively. After the recommended two dose series for PedVaxHib the geometric mean titer was 0.84 µg/mL and 50% had ≥1.0 µg/mL.

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Antibody persistence to the age of the recommended booster dose (15 to 18 months) was examined in 141 French children, after immunization at 3, 4, and 5 months of age. After the primary immunization series the GMT for anti-PRP antibody was 4.31 μ g/mL, and 88.2% had \geq 1 μ g/mL. At 18 months immediately prior to booster immunization the antibody level was 1.22 μ g/mL and 54% had \geq 1 μ g/mL. Similar results were observed in the comparative trial in Tennessee, where the GMT was 0.55 μ g/mL at 15 months of age and 21.49 μ g/mL 1 month later after the booster.

It is important to know that the conjugate vaccine will induce a memory type response in infants, so that upon exposure to the native polysaccharide a rapid antibody response may occur. This also helps confirm the T-cell dependent nature of the response. Administration of pure polysaccharide vaccine at 14 months of age after the primary immunization series at 4 and 6 months of age in Finnish children confirmed that ActHIB™ had primed for an anamnestic response to the polysaccharide. In 24 Finnish children the anti-Haemophilus b polysaccharide antibody levels at 14 and 15 months were 1.8 and 29.4 ug/mL with 66.7 and 95.7 percent of the children having ≥ 1.0 ug/mL before and after immunization with the polysaccharide respectively.

Studies of the isotype distribution showed that IgG Haemophilus b antibody is increasingly predominant after the second and third doses of ActHIB™, attesting to the T-dependent characteristics of ActHIB™, and that antibody is the predominant subclass after the primary three dose immunization series.

ActHIB™ vaccine-induced antibody is functionally effective. Complement mediated bactericidal and opsonic activity were present in serum after vaccination. Post-immunization bactericidal and PRP antibody titers were statistically correlated. In comparative assays, bactericidal activity of ActHIB™ induced antibody was found to be similar to that reported with the two other US. vaccines licensed for infants. In studies by Schlesinger et al. (1992) they found that the mean avidity of antibodies induced by ActHIB was somewhat lower than for HibTITER, 1.9 nM⁻¹ (28% \geq 2.50 nM⁻¹) versus 2.6 nM⁻¹.(52% \geq 2.50 nM⁻¹), and the bactericidal titers were directly correlated with the avidity. Sera with avidities of \geq 2.50 nM⁻¹ required 6.6 fold less antibody for similar bactericidal activity.

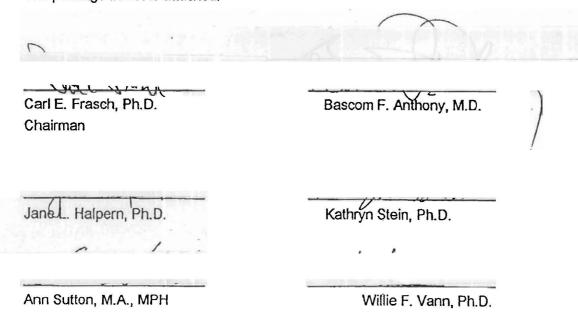
Immunogenicity in toddlers: In three US trials in children 12 to 15 months of age and in one trial in 17 to 24 month-olds, a single dose of ActHIB™ produced an antibody response comparable to that achieved by the 3 dose primary immunization series in infants. In 256 children 12 to 15 months of age the mean antibody levels increased from 0.06 to 5.12 ug/mL. Ninety percent of these children had ≥ 1 ug/mL of antipolysaccharide antibody after immunization.

C. Advisory Committee Considerations: Data regarding the manufacture, immunogenicity and safety of Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) were discussed at length at two meetings of the Vaccines and Related Biological Products Advisory Committee on September 5, 1991 and October 28, 1992. It was the consensus of the Committee at the 1991 meeting that immune surrogates could be used to show clinical potency in infants. At the 1992 meeting it was the Committee's opinion that Pasteur Merieux had satisfactorily demonstrated safety and effectiveness of the ActHIB™ vaccine using these surrogates.

D. <u>Adequacy of labeling</u>: The labeling for the Pasteur Merieux Haemophilus b conjugate vaccine is appropriate for the product and indication.

VI. APPROVED PACKAGE INSERT:

The package insert is attached.



Key references:

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- S.B. Black, H.R. Shinefield, B. Fireman, R. Hiatt, M. Polen, E. Vittinghoff, and North CA Kaiser Perm Vaccine Sty Ctr, Efficacy in infancy of oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) vaccine in a United States population of 61 080 children, <u>Pediatr. Infect. Dis. J., 10</u>:97 (1991).
- M. Santosham, M. Wolff, R. Reid, M. Hohenboken, M. Bateman, J. Goepp, M. Cortese, D. Sack, J. Hill, W. Newcomer, L. Capriotti, J. Smith, M. Owen, S. Gahagan, D. Hu, R. Kling, L. Lukacs, R.W. Ellis, P.P. Vella, G. Calandra, H. Matthews, and V. Ahonkhai, The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex, N. Engl. J. Med.;324:1767 (1991).
- C. Chu, R. Schneerson, J. B. Robbins, S. C. Rastogi, Further studies on the immunogenicity of *Haemophilus influenzae* type b and pneumococcal type 6A polysaccharide-protein conjugates, <u>Infect. Immun.</u> 40: 245, (1983).
- D.M. Granoff, E.L. Anderson, M.T. Osterholm, S.J. Holmes, J.E. McHugh, R.B. Belshe, F. Medley, and T.V. Murphy, Differences in the immunogenicity of three Haemophilus influenzae type b conjugate vaccines in infants, <u>J. Pediatr.,121</u>:187 (1992).
- M.D. Decker, K.M. Edwards, R. Bradley, and P. Palmer, Comparative trial in infants of four conjugate Haemophilus influenzae type b vaccines, <u>J. Pediatr., 120</u>:184 (1992).
- 6. R. Body, E.R. Moxon, J.A. MacFarlane, R.T. Mayon-White, and M.P.E. Slack. Efficacy of *Haemophilus influenzae* type b conugate vaccine in Oxford region. Lancet 340:847, 1992.
- 7. Schlesinger, Y. D.M. Granoff, and the Vaccine Study Group. Avidity and bactericidal activity of antibody elicited by different Haemophilus influenzae type b conjugate vaccines. <u>JAMA 267</u>:1489, 1992

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Table 1. Release specifications for Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Pasteur Merieux

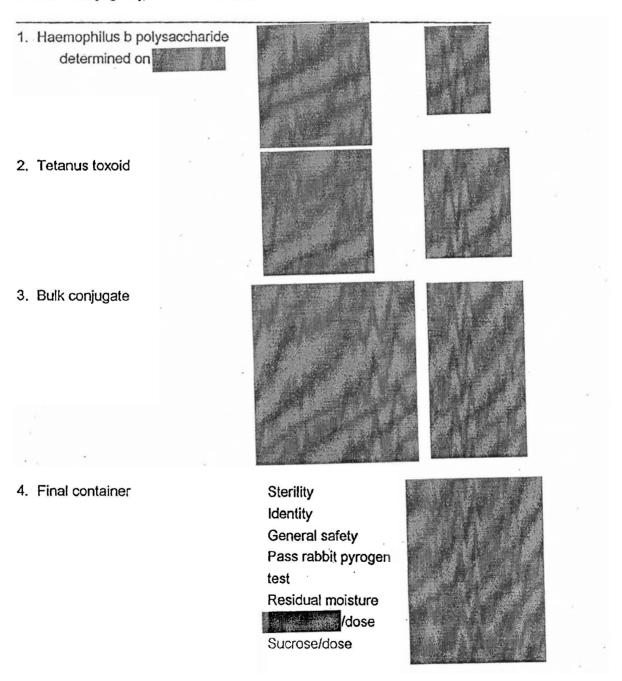


Table 2. Summary of studies for safety pertaining to use of ActHIB™ in the United States

| | Age (mo) | Other | Total subjects receiving ActHIB™ | | | | Route | Country |
|----------------|----------|----------|----------------------------------|--------|-------|-------|-------|----------|
| Study | | vaccines | Combined * | | Alone | Total | | |
| ČLI-1 | 12 | none | 0 | 0 | 36 | 36 | IM | USA |
| CLI-2 | 12 to 15 | none | o | o | 256 | 256 | IM | USA |
| CLI-3 | 15 to 17 | none | 0 | 0 | 50 | 50 | IM | USA |
| CLI-4 | 17 to 24 | none | 0 | 0 | 134 | 134 | IM | USA |
| NIH, TN | 2 | DTP | 0 | 65 | 0 | 65 | IM | USA |
| UCLA, efficacy | 2 | DTP | 0 | 5212 | 0 | 5212 | IM | USA |
| NC efficacy | 2 | DTP | 0 | 760 ** | 60 ** | 820 | IM | USA |
| Multicenter | 2 | DTP | . 0 | 365 | 0. | 365 | IM | USA |
| CLI-5 | 2 | DTP | 152 | 148 | 0 | 300 | IM | USA |
| CLI-6 | 2 | DTP | 45 | 45 . | 0 | 90 | IM | USA |
| Canada | 2 | DTP | 220 | 222 | 0 | 442 | IM | Canada # |
| Chile | 2 | DTP | 94 | 92 | 0 | 186 | SC | Chile # |
| | | Totals: | 511 | 6909 | 536 | 7956 | | |

^{*} ActHIB™ was in most studies administered at a separate site from DTP, but four studies included some individuals who received ActHIB™ combined in the same syringe with Connaught Laboratories, Inc. DTP, a formulation not currently approved.

^{**} In the NIH sponsored trial in North Carolina, for each adverse reaction, the number of individuals examined varied, and thus the numbers shown are approximate.

[#] Children in Canada and Chile received vaccine using the USA immunzation schedule at 2, 4, and 6 months of age at separate sites from DTP, excepting those who received a combined vaccine.

Table 3. Multicenter evaluation of ActHIB™ given simultaneously with DTP for safety and immunogenicity - Percent local and systemic reactions observed 24 hours after immunization

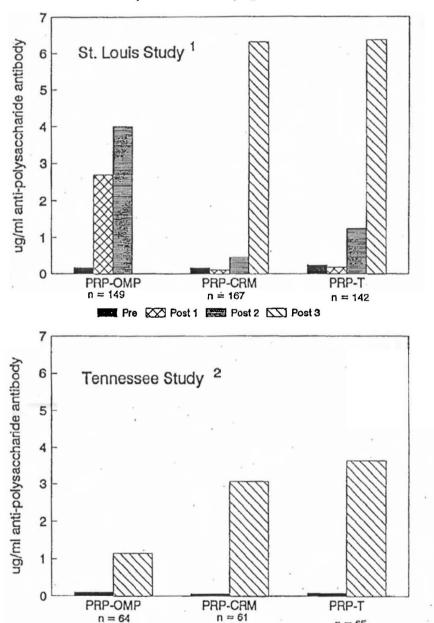
| | Dose 1 | Dose 2 | Dose 3 |
|--------------------|--------|--------|------------|
| Number: | 365 | 364 | 365 |
| Local Reactions | | | |
| Redness: | | | G20 204 |
| Any | 4.1 | 5,8 | 6.9 |
| > 1 inch | 0 | 0.8 | 0.8 |
| Swelling | 6.3 | 4.7 | 3,8 |
| Tenderness | 11.5 | 7.4 | 6 |
| Systemic Reactions | | | |
| Temperature | | | |
| 100.8-102 | 1.1 | 5.5 | 8.0 |
| >102.0 | 0.3 | 1.1 | 0.8 |
| Irritability | 21.9 | 25 | 25.2 |
| Drowsiness | 29.9 | 18.1 | 13.4 |
| Anorexia | 5.8 | 5 | 4.9 |
| Diarrhea | 6.6 | 4.7 | 6.3 |
| Vomiting | 4.1 | 3.3 | 2.7 |
| Rhinorrhea | 5.5 | 12.1 | 11.8 |
| | 6.9 | 9.4 | 5.2 |
| Cough | | | |
| Rash | 0.3 | 0 | 0.8 |

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Table 4. Some items including immunological surrogates used in evaluation of the Pasteur Merieux Haemophilus b Conjugate Vaccine

- 1. Demonstration of safety.
- 2. Randomized comparative study with currently licensed vaccines in infants for demonstration of comparable immunogenicity. The primary comparison would be seroconversion rates to 0.15 μg/ml and 1.0 μg/ml after the primary immunization series. The antibody assays sould be done in the same laboratory.
- Examination of antibody persistence to the age of the recommended booster dose.
- Demonstration that the vaccine primes the infants for a subsequent booster response to the native polysaccharide. The polysaccharide should be given 6 months or more after completion of the primary immunization series.
- 5. Determination of the IgG, IgM, and IgG subclass response following primary immunization series.
- 6. Demonstration of functional capacity of conjugate-induced antibodies by opsonic or bactericidal assay in young children.

Figure 1. Comparative antibody responses to three different Haemophilus b conjugate vaccines



PRP-OMP = PedVaxHib, Merck PRP-T = ActHIB, Pasteur Merieux

PRP-CRM = HibTITER, Praxis Biologics

n = 65

- 1. Granoff et al. J. Pediatr. 121:187, 1992
- 2. Decker et al. J. Pediatr. 120:184, 1992

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EXHIBIT 239

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HIBERIX safely and effectively. See full prescribing information for HIBERIX.

HIBERIX [Haemophilus b Conjugate Vaccine (Tetanus ToxoidConjugate)] for injection, for intramuscular use

Initial U.S. Approval: 2009

-----RECENT MAJOR CHANGES ----

Indications and Usage (1)

04/2018

----- INDICATIONS AND USAGE----

HIBERIX is a vaccine indicated for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b. HIBERIX is approved for use in children aged 6 weeks through 4 years (prior to fifth birthday). (1)

----DOSAGE AND ADMINISTRATION ----

For intramuscular administration only.

A 4-dose series (0.5-mL each) given by intramuscular injection (2.3):

- Primary series: One dose each at 2, 4, and 6 months of age. The first dose may be given as early as 6 weeks of age.
- Booster: One dose at 15 through 18 months of age.

Do not mix HIBERIX with any other vaccine in the same syringe or vial. (2.2)

----- DOSAGE FORMS AND STRENGTHS---

Solution for injection supplied as a vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent. A single dose, after reconstitution, is 0.5 mL. (3)

--- CONTRAINDICATIONS --

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any *H. influenzae* type b- or tetanus toxoid-containing vaccine or any component of HIBERIX. (4)

- WARNINGS AND PRECAUTIONS -

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give HIBERIX should be based on potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of
 injectable vaccines, including HIBERIX. Procedures should be in place to
 avoid falling injury and to restore cerebral perfusion following syncope.
 (5.2)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including HIBERIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.3)

---- ADVERSE REACTIONS ----

Common solicited adverse reactions (\geq 20%) were pain and redness at the injection site, irritability, drowsiness, fever, loss of appetite, fussiness, and restlessness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HIBERIX is indicated for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* (*H. influenzae*) type b. HIBERIX is approved for use in children aged 6 weeks through 4 years (prior to fifth birthday).

The evaluation of effectiveness of HIBERIX was based on immune responses in children using serological endpoints that predict protection from invasive disease due to *H. influenzae* type b [see Clinical Pharmacology (12.1), Clinical Studies (14.1)].

2 DOSAGE AND ADMINISTRATION

2.1 Reconstitution

HIBERIX is to be reconstituted only with the accompanying saline diluent. The reconstituted vaccine should be a clear and colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.



Lyophilized Vaccine





Figure 1. Cleanse both vial stoppers.
Withdraw 0.6 mL of saline diluent from accompanying vial.

Figure 2. Transfer 0.6 mL saline diluent into lyophilized vaccine vial.

Figure 3. Shake the vial well.

Figure 4. After reconstitution, withdraw 0.5 mL of reconstituted vaccine and administer intramuscularly.

Use a separate sterile needle and sterile syringe for each individual.

After reconstitution, administer HIBERIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and administer within 24 hours. If the vaccine is not administered immediately, shake the solution well again before administration.

2.2 Administration

For intramuscular use only.

HIBERIX is administered as a single dose (0.5 mL) by intramuscular injection into the anterolateral aspect of the thigh or deltoid.

Do not administer this product intravenously, intradermally, or subcutaneously.

If HIBERIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. HIBERIX should not be mixed with any other vaccine in the same syringe or vial.

2.3 Dose and Schedule

HIBERIX is administered as a 4-dose series (0.5-mL each dose) given by intramuscular injection. The series consists of a primary immunization course of 3 doses administered at 2, 4, and 6 months of age, followed by a booster dose administered at 15 through 18 months of age. The first dose may be given as early as 6 weeks of age.

3 DOSAGE FORMS AND STRENGTHS

HIBERIX is a solution for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent. A single dose, after reconstitution, is 0.5 mL.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any *H. influenzae* type b- or tetanus toxoid-containing vaccine or any component of the vaccine is a contraindication to administration of HIBERIX [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including HIBERIX, should be based on careful consideration of the potential benefits and possible risks.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including HIBERIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including HIBERIX, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

5.4 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine hypersensitivity. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

5.5 Altered Immunocompetence

Safety and effectiveness of HIBERIX in immunosuppressed children have not been evaluated. If HIBERIX is administered to immunosuppressed children, including children receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.6 Interference with Laboratory Tests

Urine antigen detection may not have a diagnostic value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of a *H. influenzae* type b-containing vaccine, including HIBERIX [see Drug Interactions (7.1)].

5.7 Tetanus Immunization

Immunization with HIBERIX does not substitute for routine tetanus immunization.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of HIBERIX could reveal adverse reactions not observed in clinical trials.

Across clinical trials, common solicited adverse reactions ($\geq 20\%$) were pain and redness at the injection site, irritability, drowsiness, fever, loss of appetite, fussiness, and restlessness.

Study 1: In a randomized, controlled clinical trial conducted in the U.S., children were vaccinated with HIBERIX (n = 2,963), a U.S.-licensed monovalent Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA) (n = 520), or a U.S.-licensed combined Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate Vaccine (DTaP-IPV/Hib) (Sanofi Pasteur Ltd.) (n = 520) at 2, 4, and 6 months of age. HIBERIX and Control PRP-T (Sanofi Pasteur SA) were administered concomitantly with PEDIARIX (DTaP-HBV-IPV) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] and Pneumococcal 13-valent Conjugate Vaccine (PCV13) (Wyeth Pharmaceuticals Inc.) with Doses 1, 2, and 3 and ROTARIX [Rotavirus Vaccine, Live, Oral] with Doses 1 and 2. DTaP-IPV/Hib was administered concomitantly with PCV13 and ENGERIX-B [Hepatitis B Vaccine (Recombinant)] with Doses 1, 2, and 3 and ROTARIX with Doses 1 and 2. If a birth dose of hepatitis B vaccine was received, ENGERIX-B was given with Doses 1 and 3. In the total population, 51.2% were male; 61% were white, 8% were Asian, 9% were black, and 22% were other racial/ethnic groups.

In Study 1, children received a booster dose of either HIBERIX (n = 2,336), a Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA) (n = 435), or a combined Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate Vaccine (DTaP-IPV/Hib) (Sanofi Pasteur Ltd.) (n = 400) at 15 to 18 months of age (mean age: 15.6 months) following primary vaccination at 2, 4, and 6 months of age with the same vaccine. The booster dose of HIBERIX and Control PRP-T (Sanofi Pasteur

SA) was administered concomitantly with INFANRIX (DTaP) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

In 7 additional clinical studies, 1,008 children received HIBERIX as a booster dose following primary vaccination with either HIBERIX (n = 530), Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA) (n = 235), Haemophilus b Conjugate Vaccine (Merck & Co., Inc.) (n = 26), or Haemophilus b Conjugate Vaccine (Wyeth Pharmaceuticals Inc.) (no longer licensed in the U.S., n = 217). None of the studies included a comparator group that received a booster dose with a U.S.-licensed Haemophilus b Conjugate Vaccine. Studies were conducted in Europe, Canada, and Latin America. Across these studies, the mean age of subjects at the time of booster vaccination with HIBERIX ranged from 16 to 19 months. At the time of vaccination, 172 (17.1%) subjects were aged 11 to 14 months, 642 (63.7%) subjects were aged 15 to 18 months, and 194 (19.2%) subjects were aged 19 to 25 months. Approximately half of the subjects were male. Among subjects for whom information on race/ethnicity was available, nearly all subjects were white.

In these 7 studies, HIBERIX was administered concomitantly with non-U.S. formulations (containing 2.5 mg 2-phenoxyethanol per dose as preservative) of one of the following U.S.-licensed vaccines: INFANRIX (DTaP) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed], KINRIX (DTaP-IPV) [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine], or PEDIARIX (DTaP-HBV-IPV). In the studies, DTaP-IPV and DTaP-HBV-IPV were administered in dosing regimens not approved in the U.S. Some subjects received DTaP-HBV (GlaxoSmithKline Biologicals, not licensed in U.S.) concomitantly with HIBERIX.

Solicited Adverse Reactions

The reported frequencies of solicited local reactions and general adverse reactions from Study 1 after primary and booster vaccination are presented in Table 1 and Table 2, respectively.

Table 1. Percentage of Children with Solicited Local Reactions and General Adverse Reactions within 4 Days of Primary Series Vaccination^a (at 2, 4, and 6 Months of Age) with HIBERIX^b, Control PRP-T^b, or DTaP-IPV/Hib^c, Total Vaccinated Cohort^d

| IIIDEKIA, COMITOTI KI | | HIBERI | , , | | trol PR | | DTaP-IPV/Hib | | |
|------------------------------------|-------|--------|-------|-----|---------|-----|--------------|------|-----|
| | | % | | % | | % | | | |
| | | Dose | T | | Dose | T | | Dose | |
| Adverse Reactions | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Locale | | | | | | | | | |
| n | 2,828 | 2,668 | 2,553 | 498 | 481 | 463 | 492 | 469 | 443 |
| Pain | 49 | 45 | 43 | 57 | 53 | 48 | 58 | 50 | 49 |
| Pain, Grade 3 ^f | 4 | 3 | 2 | 9 | 5 | 4 | 9 | 3 | 3 |
| Redness | 19 | 25 | 29 | 24 | 32 | 30 | 26 | 31 | 37 |
| Redness, >20 mm | 1 | 1 | 1 | 2 | 1 | 0 | 2 | 2 | 2 |
| Swelling | 13 | 15 | 19 | 19 | 22 | 20 | 20 | 24 | 24 |
| Swelling, >20 mm | 2 | 1 | 1 | 4 | 3 | 1 | 4 | 2 | 2 |
| General | | | | | | | | | |
| n | 2,830 | 2,669 | 2,553 | 499 | 480 | 463 | 492 | 469 | 443 |
| Irritability | 69 | 70 | 67 | 76 | 71 | 67 | 73 | 67 | 69 |
| Irritability, Grade 3 ^g | 4 | 6 | 5 | 8 | 8 | 5 | 6 | 5 | 3 |
| Drowsiness | 60 | 54 | 49 | 66 | 56 | 50 | 61 | 52 | 50 |
| Drowsiness, Grade 3 ^h | 2 | 3 | 2 | 4 | 2 | 1 | 4 | 3 | 3 |
| Loss of appetite | 29 | 28 | 28 | 33 | 32 | 27 | 34 | 24 | 24 |
| Loss of appetite, | 1 | 2 | 2 | 2 | 1 | 0 | 1 | 0 | 1 |
| Grade 3 ⁱ | | | | | | | | | |
| Fever | 14 | 19 | 19 | 16 | 19 | 16 | 12 | 11 | 18 |
| Fever, Grade 3 ^j | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 |

n = All subjects for whom safety data were available.

^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

^b Each dose (Doses 1, 2, and 3) of HIBERIX or Control PRP-T (Sanofi Pasteur SA) was concomitantly administered with PEDIARIX (DTaP-HBV-IPV) and PCV13. Doses 1 and 2 were concomitantly administered with ROTARIX.

^c Each dose (Doses 1, 2, and 3) of DTaP-IPV/Hib was concomitantly administered with PCV13 and ENGERIX-B with Doses 1, 2, and 3 and ROTARIX with Doses 1 and 2. If a birth dose of hepatitis B vaccine was received, ENGERIX-B was given with Doses 1 and 3.

^d Study 1: NCT01000974.

^e Local reactions at the injection site for HIBERIX, Control PRP-T, or DTaP-IPV/Hib.

f Grade 3 pain defined as cried when limb was moved/spontaneously painful.

^g Grade 3 irritability defined as crying that could not be comforted/prevented normal activity.

^h Grade 3 drowsiness defined as prevented normal daily activity.

ⁱ Grade 3 loss of appetite defined as did not eat at all.

Table 2. Percentage of Children with Solicited Local Reactions and General Adverse Reactions within 4 Days of Booster Vaccination^a (Dose 4 at 15 through 18 Months of Age) with HIBERIX^b, Control PRP-T^b, or DTaP-IPV/Hib, Total Vaccinated Cohort^c

| | HIBERIX | | Control PRP-T | | DTaP-IPV/Hib% | |
|--------------------------|------------------|----------------------|---------------|----------------------|---------------|----------------------|
| | | <u>/o</u> | 0 | <u>/o</u> | | |
| Adverse Reactions | Any | Grade 3 ^d | Any | Grade 3 ^d | Any | Grade 3 ^d |
| Locale | n = 2,224 | | n = 416 | | n = 379 | |
| Pain | 41 | 1 | 43 | 1 | 43 | 2 |
| Redness | 30 | 0 | 31 | 1 | 30 | 3 |
| Swelling | 18 | 1 | 20 | 1 | 20 | 3 |
| General | $\mathbf{n} = 1$ | 2,225 | n = 416 | | n = 379 | |
| Irritability | 58 | 2 | 60 | 5 | 53 | 2 |
| Drowsiness | 39 | 1 | 39 | 3 | 31 | 0 |
| Loss of appetite | 28 | 1 | 34 | 2 | 22 | 1 |
| Fever ^f | 15 | 1 | 14 | 1 | 18 | 1 |

n = All subjects for whom safety data were available.

Subjects received primary vaccination at 2, 4, and 6 months of age with the same vaccine as the booster dose.

Grade 3 redness, swelling defined as >20 mm.

Grade 3 irritability defined as crying that could not be comforted/prevented normal activity.

Grade 3 drowsiness defined as prevented normal daily activity.

Grade 3 loss of appetite defined as did not eat at all.

Grade 3 fever defined as >102.2°F (>39.0°C) axillary.

In an open-label, multicenter study conducted in Germany (Study 2), 371 children received a booster dose of HIBERIX administered concomitantly with DTaP-HBV-IPV. The mean age at the time of vaccination was 16 months. Subjects in this study had previously received a primary series with either HIBERIX (n = 92), Control PRP-T (Sanofi Pasteur SA) (n = 96), or Haemophilus b Conjugate Vaccine (Wyeth Pharmaceuticals Inc.) (no longer licensed in the U.S.)

j Fever defined as ≥100.4°F (≥38.0°C) rectally; Grade 3 fever defined as >103.1°F (>39.5°C) rectally.

^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

^b The booster dose of HIBERIX and Control PRP-T (Sanofi Pasteur SA) was concomitantly administered with INFANRIX (DTaP).

^c Study 1: NCT01000974.

^d Grade 3 pain defined as cried when limb was moved/spontaneously painful.

^e Local reactions at the injection site for HIBERIX, Control PRP-T, or DTaP-IPV/Hib.

^f Fever defined as ≥ 99.5 °F (≥ 37.5 °C) axillary.

(n = 183). All subjects previously received 3 doses of DTaP-HBV-IPV. The reported frequencies of solicited local reactions and general adverse reactions are presented in Table 3.

Table 3. Percentage of Children with Solicited Local Reactions and General Adverse Reactions within 4 Days of Booster Vaccination^a (Dose 4) with HIBERIX^b Coadministered with DTaP-HBV-IPV^c, Intent-to-Treat Cohort (n = 371)

| | 0/0 | % |
|--------------------|-----|----------------|
| Adverse Reactions | Any | Grade 3 |
| Locald | | |
| Redness | 25 | 2 ^e |
| Pain | 21 | 1 ^f |
| Swelling | 15 | 2 ^e |
| General | | |
| Fever ^g | 35 | 4 |
| Fussiness | 26 | 1 ^h |
| Loss of appetite | 23 | 1^{i} |
| Restlessness | 22 | 1^{i} |
| Sleepiness | 20 | 1 ⁱ |
| Diarrhea | 15 | 1 ⁱ |
| Vomiting | 5 | 1 ⁱ |

n = All subjects for whom safety data were available.

Serious Adverse Reactions

In Study 1, one of 2,963 subjects who received HIBERIX and coadministered vaccines given at 2, 4, and 6 months of age experienced a serious adverse reaction which was in temporal association with vaccination and had no alternative plausible causes (convulsion on Day 14 after Dose 1). One of 2,336 subjects who received a booster dose of HIBERIX concomitantly with

^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

^b In this study, 92 subjects previously received 3 doses of HIBERIX, 96 subjects previously received 3 doses of a Control PRP-T (Sanofi Pasteur SA), and 183 subjects previously received 3 doses of a Haemophilus b Conjugate Vaccine that is no longer licensed in the U.S.

^c In this study, DTaP-HBV-IPV was given to subjects who previously received 3 doses of DTaP-HBV-IPV. In the U.S., PEDIARIX is approved for use as a 3-dose primary series; use as a fourth consecutive dose is not approved in the U.S.

^d Local reactions at the injection site for HIBERIX.

^e Grade 3 redness or swelling defined as >20 mm.

^f Grade 3 pain defined as causing crying when limb moved.

g Fever defined as ≥100.4°F (≥38.0°C) rectally or ≥99.5°F (≥37.5°C) axillary, oral, or tympanic; Grade 3 fever defined as >103.1°F (>39.5°C) rectally or >102.2°F (>39.0°C) axillary, oral, or tympanic.

^h Grade 3 fussiness defined as persistent crying and could not be comforted.

ⁱ Grade 3 for these symptoms defined as preventing normal daily activity.

INFANRIX experienced a serious adverse reaction which was in temporal association with vaccination and had no alternative plausible causes (new onset febrile seizure on Day 1 after Dose 4).

In the 7 additional studies, 2 of 1,008 subjects reported a serious adverse reaction that occurred in the 31-day period following booster immunization with HIBERIX. One subject developed bilateral pneumonia 9 days post-vaccination and one subject experienced asthenia following accidental drug ingestion 18 days post-vaccination.

6.2 Postmarketing Experience

In addition to reports in clinical trials for HIBERIX, the following adverse reactions have been identified during postapproval use of HIBERIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccination.

General Disorders and Administration Site Conditions

Extensive swelling of the vaccinated limb, injection site induration.

Immune System Disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema.

Nervous System Disorders

Convulsions (with or without fever), hypotonic-hyporesponsive episode (i.e., sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanosis), somnolence, syncope, or vasovagal responses to injection.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea [see Warnings and Precautions (5.3)].

Skin and Subcutaneous Tissue Disorders

Rash, urticaria.

7 DRUG INTERACTIONS

7.1 Interference with Laboratory Tests

Haemophilus b capsular polysaccharide derived from Haemophilus b Conjugate Vaccines has been detected in the urine of some vaccinees.¹ Urine antigen detection may not have a diagnostic value in suspected disease due to *H. influenzae* type b within 1 to 2 weeks after receipt of a *H. influenzae* type b-containing vaccine, including HIBERIX [see Warnings and Precautions (5.6)].

7.2 Concomitant Vaccine Administration

In clinical studies, HIBERIX was administered concomitantly with routinely recommended

pediatric vaccines [see Clinical Studies (14.2)].

7.3 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to HIBERIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

HIBERIX is not approved for use in individuals aged 5 years and older. No human or animal data with HIBERIX are available to assess vaccine-associated risks in pregnancy.

8.2 Lactation

HIBERIX is not approved for use in individuals aged 5 years and older. No human or animal data are available to assess the impact of HIBERIX on milk production, its presence in breast milk, or its effects on the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of HIBERIX in children younger than 6 weeks and in children aged 5 to 16 years have not been established.

11 DESCRIPTION

HIBERIX [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] is a solution for intramuscular injection, supplied as a sterile, lyophilized powder which is reconstituted at the time of use with the accompanying saline diluent. HIBERIX contains Haemophilus b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]), a high molecular weight polymer prepared from the *H. influenzae* type b strain 20,752 grown in a synthetic medium that undergoes heat inactivation and purification. The tetanus toxin, prepared from *Clostridium tetani* grown in a semi-synthetic medium, is detoxified with formaldehyde and purified. The capsular polysaccharide is covalently bound to the tetanus toxoid. After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer. The diluent for HIBERIX is a sterile saline solution (0.9% sodium chloride) supplied in vials.

After reconstitution, each 0.5-mL dose is formulated to contain 10 mcg of purified capsular polysaccharide conjugated to approximately 25 mcg of tetanus toxoid, 12.6 mg of lactose, and ≤0.5 mcg of residual formaldehyde.

HIBERIX does not contain a preservative.

The lyophilized vaccine and saline diluent vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

H. influenzae is a gram-negative coccobacillus. Most strains of *H. influenzae* that cause invasive disease are type b. *H. influenzae* type b can cause invasive disease such as sepsis and meningitis.

Specific levels of antibodies to polyribosyl-ribitol-phosphate (anti-PRP) have been shown to correlate with protection against invasive disease due to *H. influenzae* type b. Based on data from passive antibody studies² and a clinical efficacy study with unconjugated *Haemophilus* b polysaccharide vaccine³, an anti-PRP concentration of 0.15 mcg/mL has been accepted as a minimal protective level. Data from an efficacy study with unconjugated *Haemophilus* b polysaccharide vaccine indicate that an anti-PRP concentration of ≥1.0 mcg/mL predicts protection through at least a 1-year period.⁴,⁵ These antibody levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including HIBERIX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

HIBERIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

14.1 Immunological Evaluation

Primary Series Vaccination (Doses 1, 2, and 3)

The immunogenicity of HIBERIX was evaluated in a randomized, controlled trial (Study 1). HIBERIX or control vaccines were administered concomitantly with U.S.-licensed vaccines [see Adverse Reactions (6.1)].

Anti-PRP geometric mean concentrations (GMCs) and seroprotection rates 1 month following Dose 3 of HIBERIX, Control PRP-T (Sanofi Pasteur SA), or DTaP-IPV/Hib are presented in Table 4.

Table 4. Anti-PRP GMCs and Seroprotection Rates 1 Month following 3 Doses of HIBERIX, Control PRP-T^a, or DTaP-IPV/Hib^b Administered at 2, 4, and 6 Months of Age. ATP Cohort for Immunogenicity^c

| Vaccine | n | Anti-PRP GMC (mcg/mL) (95% CI) | % Anti-PRP ≥0.15 mcg/mL (95% CI) | % Anti-PRP ≥1.0 mcg/mL (95% CI) |
|---------------|-------|--------------------------------------|--|---------------------------------------|
| HIBERIX | 1,590 | 5.19 | 96.6 | 81.2 |
| | | (4.77, 5.66) | (95.6, 97.4) | (79.2, 83.1) |
| Control PRP-T | 274 | 6.74 | 96.7 ^d | 89.8 ^e |
| | | (5.59, 8.13) | (93.9, 98.5) | (85.6, 93.1) |
| DTaP-IPV/Hib | 253 | 3.64 | 92.5 ^f | 78.3 ^f |
| | | (2.89, 4.58) | (88.5, 95.4) | (72.7, 83.2) |

^a U.S.-licensed monovalent Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA).

Booster Vaccination (Dose 4)

The immunogenicity of HIBERIX administered as a booster dose at 15 to 18 months of age was evaluated in a subset of children from Study 1 (n = 336) in comparison with U.S.-licensed vaccines following primary vaccination at 2, 4, and 6 months of age [see Adverse Reactions (6.1)]. The booster dose of HIBERIX and Control PRP-T (Sanofi Pasteur SA) was administered concomitantly with INFANRIX.

Antibodies to PRP were measured in sera obtained immediately prior to and 1 month after booster vaccination with HIBERIX or the control vaccines. Anti-PRP GMCs and seroprotection rates are presented in Table 5.

^b U.S.-licensed DTaP-IPV/Hib Vaccine (Sanofi Pasteur Ltd.).

^c Study 1: NCT01000974.

^d HIBERIX was non-inferior to Control PRP-T for percent of subjects achieving anti-PRP ≥0.15 mcg/mL (lower limit of 95% CI on difference of HIBERIX minus Control PRP-T ≥ predefined limit of -5%).

^e The non-inferiority criterion was not met (lower limit of 95% CI for the difference in the percentages of subjects with anti-PRP ≥1.0 mcg/mL between two groups [HIBERIX minus Control PRP-T] was -12.28%, which was lower than the predefined limit of -10%).

^f Analyses of anti-PRP immune responses following DTaP-IPV/Hib vaccination were exploratory.

Table 5. Anti-PRP GMCs and Seroprotection Rates prior to and 1 Month following a Booster Dose (Dose 4 at 15 through 18 Months of Age) of HIBERIX, Control PRP-

Ta, or DTaP-IPV/Hibb, ATP Cohort for Immunogenicityc

| | | Anti-PRP GMC (mcg/mL) (95% CI) | | % Anti-PRP ≥0.15 mcg/mL (95% CI) | | % Anti-PRP ≥1.0 mcg/mL (95% CI) | |
|---------------|---------|--------------------------------------|----------------|--|---------------|---------------------------------------|-------------------|
| Vaccine | n | Pre- | Post- | Pre- | Post- | Pre- | Post- |
| HIBERIX | 329-336 | 0.50 | 48.78 | 75.1 | 100.0 | 32.2 | 99.1 |
| | | (0.42, 0.59) | (42.0, 56.66) | (70.0, 79.7) | (98.9, 100.0) | (27.2, 37.6) | (97.4, 99.8) |
| Control PRP-T | 226-236 | 0.47 | 40.29 | 76.1 | 99.6 | 27.0 | 97.9 ^d |
| | | (0.38, 0.57) | (33.39, 48.63) | (70.0, 81.5) | (97.7, 100.0) | (21.3, 33.3) | (95.1, 99.3) |
| DTaP-IPV/Hib | 175-186 | 0.38 | 37.54 | 66.3 | 100.0 | 25.1 | 98.9e |
| | | (0.30, 0.48) | (30.53, 46.16) | (58.8, 73.2) | (98.0, 100.0) | (18.9, 32.2) | (96.2, 99.9) |

^a U.S.-licensed monovalent Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA).

In 6 additional clinical studies, the immune response to HIBERIX administered as a booster dose was evaluated in a total of 415 children aged 12 to 23 months. At the time of vaccination, 30 children were aged 12 to 14 months, 316 children were aged 15 to 18 months, and 69 children were aged 19 to 23 months. Among subjects, 43% to 60% were male. Among subjects for whom information on race/ethnicity was available, nearly all subjects were white. None of the studies included a comparator group that received a booster dose with a U.S.-licensed Haemophilus b Conjugate Vaccine. Characteristics of 3 of these studies are presented in Table 6.

^b U.S.-licensed DTaP-IPV/Hib Vaccine (Sanofi Pasteur Ltd.).

^c Study 1: NCT01000974.

d HIBERIX was non-inferior to Control PRP-T for percent of subjects achieving anti-PRP ≥1.0 mcg/mL (lower limit of 97.5% CI on difference of HIBERIX minus Control PRP-T ≥predefined limit of -10%) at 1 month following the booster dose.

^e Analyses of anti-PRP immune responses following DTaP-IPV/Hib vaccination were exploratory.

Table 6. Characteristics of 3 Open-Label Booster Immunization Studies of HIBERIX

| | | Per-Protocol | | | ccination with BERIX |
|-------|---------|----------------|--------------------------------|-------------|-------------------------|
| | | Immunogenicity | | Age at | Concomitantly |
| | | Cohort | | Vaccination | Administered |
| Study | Country | n | Priming History | (months) | Vaccine ^a |
| 3 | Canada | 42 | DTaP-HBV-IPV ^b + | 16-18 | DTaP-HBV- |
| | | | Haemophilus b | | IPV^b |
| | | | Conjugate Vaccine ^c | | |
| | | | at 2, 4, and 6 months | | |
| | | | of age | | |
| 4 | Canada | 64 | DTaP-IPV ^d + | 16-19 | DTaP-IPV ^d |
| | | | HIBERIX | | |
| | | | at 2, 4, and 6 months | | |
| | | | of age | | |
| 5 | Germany | 108 | DTaP-HBV ^e + | 16-23 | DTaP-HBV ^e |
| | | | HIBERIX | | |
| | | | at 3, 4, and 5 months | | |
| | | | of age | | |

^a Administered at a separate site.

Antibodies to PRP were measured in sera obtained immediately prior to and 1 month after booster vaccination with HIBERIX. Geometric mean concentrations and anti-PRP seroprotection rates are presented in Table 7.

^b Non-U.S. formulation equivalent to PEDIARIX with the exception of containing 2.5 mg 2-phenoxyethanol per dose as preservative. In the U.S., PEDIARIX is approved for use as a 3-dose primary series; use as a fourth consecutive dose is not approved in the U.S.

^c U.S.-licensed Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA).

^d Non-U.S. formulation equivalent to KINRIX with the exception of containing 2.5 mg 2-phenoxyethanol per dose as preservative. In the U.S., KINRIX is approved for use as the fifth dose of DTaP and the fourth dose of IPV in children aged 4 to 6 years previously primed with approved dosing regimens of INFANRIX and/or PEDIARIX. The DTaP-IPV dosing regimen is not approved in the U.S.

^e Manufactured by GlaxoSmithKline Biologicals (not licensed in the U.S.).

Table 7. Anti-PRP GMCs and Seroprotection Rates prior to and 1 Month following a Booster Dose of HIBERIX, Per-Protocol Immunogenicity Cohort

| | | Anti-PRP GMC (mcg/mL) | | % Anti-PRP ≥0.15 mcg/mL | | % Anti-PRP ≥1.0 mcg/mL | |
|----------------|-------|-----------------------|-------|----------------------------|-------|---------------------------|-------|
| Study | n | Pre- | Post- | Pre- | Post- | Pre- | Post- |
| 3 ^a | 42 | 0.46 | 59.07 | 76.2 | 100 | 35.7 | 97.6 |
| 4 ^b | 63-64 | 0.25 | 47.78 | 71.4 | 100 | 12.7 | 100 |
| 5° | 108 | 0.59 | 96.12 | 77.8 | 100 | 32.4 | 100 |

GMC = Geometric mean antibody concentration.

n = Number of children for whom serological results were available for the pre- and post-dose immunological evaluations.

Studies 3, 4, and 5 correspond to Studies 3, 4, and 5, respectively in Table 6.

- ^a Canadian study in children aged 16 to 18 months who previously received 3 doses of DTaP-HBV-IPV and Haemophilus b Conjugate Vaccine (Control PRP-T) (Sanofi Pasteur SA). The booster dose of HIBERIX was coadministered with DTaP-HBV-IPV (a fourth consecutive dose of PEDIARIX is not approved in the U.S.). In this study, pre-vaccination sera may have been obtained up to 1 week prior to booster vaccination with HIBERIX.
- ^b Canadian study in children aged 16 to 19 months who previously received 3 doses of DTaP-IPV and HIBERIX. The booster dose of HIBERIX was coadministered with DTaP-IPV. The DTaP-IPV dosing regimen is not approved in the U.S.
- ^c German study in children aged 16 to 23 months who previously received 3 doses of DTaP-HBV (GlaxoSmithKline Biologicals, not licensed in the U.S.) and HIBERIX. The booster dose of HIBERIX was coadministered with DTaP-HBV.

14.2 Concomitant Vaccine Administration

Primary Series Vaccination (Doses 1, 2, and 3)

In U.S. Study 1, subjects who received HIBERIX concomitantly with PEDIARIX (DTaP-HBV-IPV) and PCV13 at 2, 4, and 6 months of age had no evidence for reduced antibody responses relative to the response in control subjects administered Control PRP-T (Sanofi Pasteur SA) concomitantly with PEDIARIX (DTaP-HBV-IPV) and PCV13, to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, and pertactin), diphtheria toxoid (antibody levels ≥0.1 IU/mL), tetanus toxoid (antibody levels ≥0.1 IU/mL), poliovirus types 1, 2, and 3 (antibody levels ≥1:8 to each virus), PCV13 (antibody levels ≥0.2 mcg/mL and GMC to each serotype), or hepatitis B (anti-hepatitis B surface antigen ≥10 mIU/mL). The immune responses to PEDIARIX (DTaP-HBV-IPV) and PCV13 were evaluated 1 month following Dose 3. Subjects in both groups received ROTARIX at 2 and 4 months of age.

Booster Vaccination (Dose 4)

In U.S. Study 1, subjects who received a booster dose of HIBERIX concomitantly with INFANRIX at 15 to 18 months of age had no evidence for reduced antibody responses to pertussis antigens (GMC to pertussis toxin, filamentous hemagglutinin, and pertactin), diphtheria

toxoid (antibody levels ≥0.1 IU/mL), and tetanus toxoid (antibody levels ≥0.1 IU/mL), relative to the responses in control subjects administered Control PRP-T (Sanofi Pasteur SA) concomitantly with INFANRIX.

In 7 additional studies, a booster dose of HIBERIX was administered concomitantly with non-U.S. formulations of INFANRIX, KINRIX, and PEDIARIX. Non-U.S. formulations of KINRIX and PEDIARIX were administered in dosing regimens not approved in the U.S.

Sufficient data are not available to confirm lack of interference in immune responses to vaccines other than INFANRIX administered concomitantly with a booster dose of HIBERIX.

15 REFERENCES

- 1. Rothstein EP, Madore DV, Girone JAC, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. *Pediatr Infect Dis J.* 1991;10:311-314.
- 2. Robbins JB, Parke JC, Schneerson R, et al. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. *Pediatr Res.* 1973;7:103-110.
- 3. Peltola H, Käythy H, Sivonen A, et al. *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: A double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. *Pediatrics*. 1977;60:730-737.
- 4. Käythy H, Peltola H, Karanko V, et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis.* 1983;147:1100.
- 5. Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis.* 1984;149:1034.

16 HOW SUPPLIED/STORAGE AND HANDLING

HIBERIX is available in single-dose vials of lyophilized vaccine, accompanied by vials containing 0.85 mL of saline diluent (packaged without syringes or needles).

Supplied as package of 10 doses (NDC 58160-818-11):

NDC 58160-816-01 Vial of lyophilized vaccine in Package of 10: NDC 58160-816-05

NDC 58160-817-01 Vial of saline diluent in Package of 10: NDC 58160-817-05

16.1 Storage before Reconstitution

Lyophilized vaccine vials: Store refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light.

Diluent: Store refrigerated or at controlled room temperature between 2° and 25°C (36° and 77°F). Do not freeze. Discard if the diluent has been frozen.

16.2 Storage after Reconstitution

Administer within 24 hours of reconstitution. After reconstitution, store refrigerated between 2° and 8°C (36° and 46°F). Discard the reconstituted vaccine if not used within 24 hours. Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

- Inform parents or guardians of the potential benefits and risks of immunization with HIBERIX.
- Inform parents or guardians about the potential for adverse reactions that have been temporally associated with administration of HIBERIX or other vaccines containing similar components.
- Give parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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HRX:XPI

EXHIBIT 240

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Liquid PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

DESCRIPTION

PedvaxHIB[®] [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] is a highly purified capsular polysaccharide (polyribosylribitol phosphate or PRP) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) that is covalently bound to an outer membrane protein complex (OMPC) of the B11 strain of *Neisseria meningitidis* serogroup B. The covalent bonding of the PRP to the OMPC which is necessary for enhanced immunogenicity of the PRP is confirmed by quantitative analysis of the conjugate's components following chemical treatment which yields a unique amino acid. The potency of PedvaxHIB is determined by assay of PRP.

Haemophilus influenzae type b and Neisseria meningitidis serogroup B are grown in complex fermentation media. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from Neisseria meningitidis is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.

Liquid PedvaxHIB is ready to use and does not require a diluent. Each 0.5 mL dose of Liquid PedvaxHIB is a sterile product formulated to contain: 7.5 mcg of Haemophilus b PRP, 125 mcg of Neisseria meningitidis OMPC and 225 mcg of aluminum as amorphous aluminum hydroxyphosphate sulfate (previously referred to as aluminum hydroxide), in 0.9% sodium chloride, but does not contain lactose or thimerosal. Liquid PedvaxHIB is a slightly opaque white suspension.

This vaccine is for intramuscular administration and not for intravenous injection. (See DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY

Prior to the introduction of Haemophilus b Conjugate Vaccines, *Haemophilus influenzae* type b (Hib) was the most frequent cause of bacterial meningitis and a leading cause of serious, systemic bacterial disease in young children worldwide. 1,2,3,4

Hib disease occurred primarily in children under 5 years of age in the United States prior to the initiation of a vaccine program and was estimated to account for nearly 20,000 cases of invasive infections annually, approximately 12,000 of which were meningitis. The mortality rate from Hib meningitis is about 5%. In addition, up to 35% of survivors develop neurologic sequelae including seizures, deafness, and mental retardation.^{5,6} Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis and pericarditis.

Prior to the introduction of the vaccine, it was estimated that 17% of all cases of Hib disease occurred in infants less than 6 months of age. The peak incidence of Hib meningitis occurs between 6 to 11 months of age. Forty-seven percent of all cases occur by one year of age with the remaining 53% of cases occurring over the next four years.^{2,20}

Among children under 5 years of age, the risk of invasive Hib disease is increased in certain populations including the following:

- Daycare attendees^{8,9}
- Lower socio-economic groups¹⁰
- Blacks¹¹ (especially those who lack the Km(1) immunoglobulin allotype)¹²
- Caucasians who lack the G2m(n or 23) immunoglobulin allotype¹³
- Native Americans^{14,15,16}
- Household contacts of cases¹⁷

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Individuals with asplenia, sickle cell disease, or antibody deficiency syndromes^{18,19}

An important virulence factor of the Hib bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Hib disease.^{3,21} While the anti-PRP level associated with protection using conjugated vaccines has not yet been determined, the level of anti-PRP associated with protection in studies using bacterial polysaccharide immune globulin or nonconjugated PRP vaccines ranged from >0.15 to >1.0 mcg/mL.²²⁻²⁸

Nonconjugated PRP vaccines are capable of stimulating B-lymphocytes to produce antibody without the help of T-lymphocytes (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent). PedvaxHIB is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier²⁹ producing an antigen which is postulated to convert the T-independent antigen (PRP alone) into a T-dependent antigen resulting in both an enhanced antibody response and immunologic memory. *Clinical Evaluation of PedvaxHIB*

PedvaxHIB, in a lyophilized formulation (lyophilized PedvaxHIB), was initially evaluated in 3,486 Native American (Navajo) infants, who completed the primary two-dose regimen in a randomized, double-blind, placebo-controlled study (The Protective Efficacy Study). At the time of the study, this population had a much higher incidence of Hib disease than the United States population as a whole and also had a lower antibody response to Haemophilus b Conjugate Vaccines, including PedvaxHIB.14,15,16,30,33

Each infant in this study received two doses of either placebo or lyophilized PedvaxHIB with the first dose administered at a mean of 8 weeks of age and the second administered approximately two months later; DTP and OPV were administered concomitantly. Antibody levels were measured in a subset of each group (TABLE 1).

| TABLE 1 Antibody Responses in Navajo Infants | | | | | | | | |
|--|-----------------|-----------------|--------------|-------------|--------------|--|--|--|
| | No. of | | % Subje | cts with | Anti-PRP GMT | | | |
| Vaccine | Subjects | Time | >0.15 mcg/mL | >1.0 mcg/mL | (mcg/mL) | | | |
| Lyophilized | 416** | Pre-Vaccination | 44 | 10 | 0.16 | | | |
| PedvaxHIB* | 416 | Post-Dose 1 | 88 | 52 | 0.95 | | | |
| | 416 | Post-Dose 2 | 91 | 60 | 1.43 | | | |
| Placebo* | 461" | Pre-Vaccination | 44 | 9 | 0.16 | | | |
| | 461 | Post-Dose 1 | 21 | 2 | 0.09 | | | |
| | 461 | Post-Dose 2 | 14 | 1 | 0.08 | | | |
| Lyophilized | 27 [†] | Prebooster | 70 | 33 | 0.51 | | | |
| PedvaxHIB | 27 | Postbooster†† | 100 | 89 | 8.39 | | | |

^{*}Post-Vaccination values obtained approximately 1–3 months after each dose.

Most subjects were initially followed until 15 to 18 months of age. During this time, 22 cases of invasive Hib disease occurred in the placebo group (8 cases after the first dose and 14 cases after the second dose) and only 1 case in the vaccine group (none after the first dose and 1 after the second dose). Following the primary two-dose regimen, the protective efficacy of lyophilized PedvaxHIB was calculated to be 93% with a 95% confidence interval of 57%-98% (p=0.001, two-tailed). In the two months between the first and second doses, the difference in number of cases of disease between placebo and vaccine recipients (8 vs. 0 cases, respectively) was statistically significant (p=0.008, two-tailed); however, a primary two-dose regimen is required for infants 2-14 months of age.

At termination of the study, placebo recipients were offered vaccine. All original participants were then followed two years and nine months from termination of the study. During this extended follow-up, invasive Hib disease occurred in an additional seven of the original placebo

[&]quot;The Protective Efficacy Study

[†] Immunogenicity Trial34

⁺⁺ Booster given at 12 months of age; Post-Vaccination values obtained 1 month after administration of booster dose.

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recipients prior to receiving vaccine and in one of the original vaccine recipients (who had received only one dose of vaccine). No cases of invasive Hib disease were observed in placebo recipients after they received at least one dose of vaccine. Efficacy for this follow-up period, estimated from person-days at risk, was 96.6% (95 C.I., 72.2-99.9%) in children under 18 months of age and 100% (95 C.I., 23.5-100%) in children over 18 months of age.³³

Since protective efficacy with lyophilized PedvaxHIB was demonstrated in such a high risk population, it would be expected to be predictive of efficacy in other populations.

The safety and immunogenicity of lyophilized PedvaxHIB were evaluated in infants and children in other clinical studies that were conducted in various locations throughout the United States. PedvaxHIB was highly immunogenic in all age groups studied.^{31,32}

Lyophilized PedvaxHIB induced antibody levels greater than 1.0 mcg/mL in children who were poor responders to nonconjugated PRP vaccines. In a study involving such a subpopulation,^{33,34} 34 children ranging in age from 27 to 61 months who developed invasive Hib disease despite previous vaccination with nonconjugated PRP vaccines were randomly assigned to 2 groups. One group (n=14) was vaccinated with lyophilized PedvaxHIB and the other group (n=20) with a nonconjugated PRP vaccine at a mean interval of approximately 12 months after recovery from disease. All 14 children vaccinated with lyophilized PedvaxHIB but only 6 of 20 children revaccinated with a nonconjugated PRP vaccine achieved an antibody level of >1.0 mcg/mL. The 14 children who had not responded to revaccination with the nonconjugated PRP vaccine were then vaccinated with a single dose of lyophilized PedvaxHIB; following this vaccination, all achieved antibody levels of >1.0 mcg/mL.

In addition, lyophilized PedvaxHIB has been studied in children at high risk of Hib disease because of genetically-related deficiencies [Blacks who were Km(1) allotype negative and Caucasians who were G2m(23) allotype negative] and are considered hyporesponsive to nonconjugated PRP vaccines on this basis.³⁵ The hyporesponsive children had anti-PRP responses comparable to those of allotype positive children of similar age range when vaccinated with lyophilized PedvaxHIB. All children achieved anti-PRP levels of >1.0 mcg/mL.

The safety and immunogenicity of Liquid PedvaxHIB were compared with those of lyophilized PedvaxHIB in a randomized clinical study involving 903 infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. The antibody responses induced by each formulation of PedvaxHIB were similar. TABLE 2 shows antibody responses from this clinical study in subjects who received their first dose at 2 to 3 months of age.

| TARLE 2 |
|--|
| INDEL 2 |
| Antibody Responses to Liquid and Lyophilized PedvaxHIB in Infants From the General U.S. Population |
| |

| | Age | • | No. of | % Subjects w | ith anti-PRP | Anti-PRP GMT |
|---------------|-----------------|-----------------|----------|--------------|--------------|--------------|
| Formulation | (Months) | Time | Subjects | >0.15 mcg/mL | >1.0 mcg/mL | (mcg/mL) |
| | | Pre-Vaccination | 487 | 32 | 7 | 0.12 |
| Liquid | 2-3 | Post-Dose 1* | 480 | 94 | 64 | 1.55 |
| PedvaxHIB | | Post-Dose 2** | 393 | 97 | 80 | 3.22 |
| (7.5 mcg PRP) | 12-15 | Prebooster | 284 | 80 | 30 | 0.49 |
| , , | | Postbooster** | 284 | 99 | 95 | 10.23 |
| | 24 [†] | Persistence | 94 | 97 | 55 | 1.29 |
| | | Pre-Vaccination | 171 | 37 | 6 | 0.13 |
| Lyophilized | 2-3 | Post-Dose 1* | 169 | 97 | 72 | 1.88 |
| PedvaxHIB | | Post-Dose 2** | 133 | 99 | 81 | 2.69 |
| (15 mcg PRP) | 12-15 | Prebooster | 87 | 71 | 28 | 0.39 |
| ` | | Postbooster** | 87 | 99 | 91 | 7.64 |
| | 24 [†] | Persistence | 37 | 97 | 54 | 1.10 |

^{*}Approximately two months Post-Vaccination

A booster dose of PedvaxHIB is required in infants who complete the primary two-dose regimen before 12 months of age. This booster dose will help maintain antibody levels during the

[&]quot;Approximately one month Post-Vaccination

[†] Approximately

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first two years of life when children are at highest risk for invasive Hib disease. (See TABLE 2 and DOSAGE AND ADMINISTRATION.)

In four United States studies, antibody responses to lyophilized PedvaxHIB were evaluated in several subpopulations of infants initially vaccinated between 2 to 3 months of age. (See TABLE 3.)

| TABLE 3 |
|--|
| Antibody Responses* |
| After Two Doses of Lyophilized PedvaxHIB Among Infants Initially Vaccinated at |
| 2-3 Months of Age By Racial/Ethnic Group |

| LYOPHILIZED | | | | | | | |
|------------------|----------|--------------|--------------|--------------|--|--|--|
| Racial/Ethnic | No. of | % Subjects W | ith Anti-PRP | Anti-PRP GMT | | | |
| Groups | Subjects | >0.15 mcg/mL | >1.0 mcg/mL | (mcg/mL) | | | |
| Native American† | 54 | 96 | 70 | 2.47 | | | |
| Caucasian | 201 | 99 | 82 | 3.52 | | | |
| Hispanic | 76 | 99 | 88 | 3.54 | | | |
| Black | 23 | 100 | 96 | 5.40 | | | |
| | | | | | | | |

One month after the second dose

In two United States studies, antibody responses to Liquid PedvaxHIB were evaluated in several subpopulations of infants initially vaccinated between 2 to 3 months of age. (See TABLE 4.)

TABLE 4 Antibody Responses* After Two Doses of Liquid PedvaxHIB Among Infants Initially Vaccinated at 2–3 Months of Age By Racial/Ethnic Group

| | | LIQUID | | |
|-------------------|----------|--------------------------|-------------|--------------|
| Racial/Ethnic | No. of | % Subjects With Anti-PRP | | Anti-PRP GMT |
| Groups | Subjects | >0.15 mcg/mL | >1.0 mcg/mL | (mcg/mL) |
| Native American** | 90 | 97 | 78 | 2.76 |
| Caucasian | 143 | 94 | 72 | 2.16 |
| Hispanic | 184 | 98 | 85 | 4.34 |
| Black | 18 | 100 | 94 | 7.58 |

One month after the second dose

Antibodies to the OMPC of *N. meningitidis* have been demonstrated in vaccinee sera, but the clinical relevance of these antibodies has not been established.³³

Interchangeability of Licensed Haemophilus b Conjugate Vaccines and PedvaxHIB

Published studies have examined the interchangeability of other licensed Haemophilus b Conjugate Vaccines and PedvaxHIB.42,43,44,45,52 According to the American Academy of Pediatrics, excellent immune responses have been achieved when different vaccines have been interchanged in the primary series. If PedvaxHIB is given in a series with one of the other products licensed for infants, the recommended number of doses to complete the series is determined by the other product and not by PedvaxHIB. PedvaxHIB may be interchanged with other licensed Haemophilus b Conjugate Vaccines for the booster dose. 52

Use with Other Vaccines

Results from clinical studies indicate that Liquid PedvaxHIB can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) or RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)].33 No impairment of immune response to individual tested vaccine antigens was demonstrated.

The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

[†] Apache and Navajo

^{**} Apache and Navajo

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In addition, a PRP-OMPC-containing product, COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with a booster dose of DTaP [diphtheria, tetanus, acellular pertussis] at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. COMVAX has also been administered concomitantly with the primary series of DTaP to a limited number of infants. PRP antibody responses are satisfactory for COMVAX, but immune responses are currently unavailable for DTaP (see Manufacturer's Product Circular for COMVAX). No serious vaccine-related adverse events were reported.³³

INDICATIONS AND USAGE

Liquid PedvaxHIB is indicated for routine vaccination against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

Liquid PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease such as meningitis or sepsis. As with any vaccine, vaccination with Liquid PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine.

BECAUSE OF THE POTENTIAL FOR IMMUNE TOLERANCE, Liquid PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 6 WEEKS OF AGE. (See PRECAUTIONS.)

Revaccination

Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine or the diluent.

Persons who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

PRECAUTIONS

General

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

As with other vaccines, Liquid PedvaxHIB may not induce protective antibody levels immediately following vaccination.

As reported with Haemophilus b Polysaccharide Vaccine³⁶ and another Haemophilus b Conjugate Vaccine³⁷, cases of Hib disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

There is insufficient evidence that Liquid PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The Advisory Committee on Immunization Practices (ACIP) has recommended that vaccination should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade

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fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.⁴⁶

If PedvaxHIB is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

Instructions to Healthcare Provider

The healthcare provider should determine the current health status and previous vaccination history of the vaccinee.

The healthcare provider should question the patient, parent, or guardian about reactions to a previous dose of PedvaxHIB or other Haemophilus b Conjugate Vaccines.

Information for Patients

The healthcare provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The healthcare provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see ADVERSE REACTIONS.

Patients, parents, and guardians should be instructed to report any serious adverse reactions to their healthcare provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.47

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB;³⁸ in clinical studies with lyophilized PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Liquid PedvaxHIB has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older.

Pediatric Use

Safety and effectiveness in infants below the age of 2 months and in children 6 years of age and older have not been established. In addition, Liquid PedvaxHIB should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen).⁴⁹⁻⁵¹ Liquid PedvaxHIB is not recommended for use in individuals 6 years of age and older because they are generally not at risk of Hib disease.

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

Liquid PedvaxHIB

In a multicenter clinical study (n=903) comparing the effects of Liquid PedvaxHIB with those of lyophilized PedvaxHIB, 1,699 doses of Liquid PedvaxHIB were administered to 678 healthy infants 2 to 6 months of age from the general U.S. population. DTP and OPV were administered concomitantly to most subjects. Both formulations of PedvaxHIB were generally well tolerated and no serious vaccine-related adverse reactions were reported.

During a three-day period following primary vaccination with Liquid PedvaxHIB in these infants, the most frequently reported (>1%) adverse reactions, without regard to causality, excluding those shown in TABLE 5, in decreasing order of frequency, were: irritability,

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sleepiness, injection site pain/soreness, injection site erythema (≤2.5 cm diameter, see also TABLE 5), injection site swelling/induration (≤2.5 cm diameter, see also TABLE 5), unusual high-pitched crying, prolonged crying (>4 hr), diarrhea, vomiting, crying, pain, otitis media, rash, and upper respiratory infection.

Selected objective observations reported by parents over a 48-hour period in these infants following primary vaccination with Liquid PedvaxHIB are summarized in TABLE 5.

TABLE 5
Fever or Local Reactions in Subjects First Vaccinated at 2 to 6 Months of Age with Liquid PedvaxHIB'

| | | Post-Dose 1 (hr) | | Post-Dose 2 (hr) | | | | |
|--|---------------------------------|---------------------|----------|---------------------|---------------------------------|------|----------|-----|
| Reaction | No. of Subjects Evaluated | 6 | 24 | 48 | No. of Subjects Evaluated | 6 | 24 | 48 |
| | | Pe | ercentaç | ge | | Pe | ercentaç | ge |
| Fever** >38.3°C (≥101°F) Rectal | 222 | 18.1 | 4.4 | 0.5 | 206 | 14.1 | 9.4 | 2.8 |
| Erythema >2.5 cm diameter | 674 | 2.2 | 1.0 | 0.5 | 562 | 1.6 | 1.1 | 0.4 |
| Swelling >2.5 cm diameter | 674 | 2.5 | 1.9 | 0.9 | 562 | 0.9 | 0.9 | 1.3 |

^{*}DTP and OPV were administered concomitantly to most subjects.

Adverse reactions during a three-day period following administration of the booster dose were generally similar in type and frequency to those seen following primary vaccination.

Lyophilized PedvaxHIB

In The Protective Efficacy Study (see CLINICAL PHARMACOLOGY), 4,459 healthy Navajo infants 6 to 12 weeks of age received lyophilized PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received lyophilized PedvaxHIB and those who received placebo, and none was reported to be related to lyophilized PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to lyophilized PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to lyophilized PedvaxHIB.

In early clinical studies involving the administration of 8,086 doses of lyophilized PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, lyophilized PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. In a subset of these infants, urticaria was reported in two children, and thrombocytopenia was seen in one child. A cause and effect relationship between these side effects and the vaccination has not been established.

Potential Adverse Reactions

The use of Haemophilus b Polysaccharide Vaccines and another Haemophilus b Conjugate Vaccine has been associated with the following additional adverse effects: early onset Hib disease and Guillain-Barré syndrome. A cause and effect relationship between these side effects and the vaccination was not established.^{36,37,39,40,41,49}

[&]quot;Fever was also measured by another method or reported as normal for an additional 345 infants after dose 1 and for an additional 249 infants after dose 2; however, these data are not included in this table.

Liquid PedvaxHIB®
[Haemophilus b Conjugate Vaccine

(Meningococcal Protein Conjugate)]

Post-Marketing Adverse Reactions

The following additional adverse reactions have been reported with the use of the lyophilized and liquid formulations of PedvaxHIB:

Hemic and Lymphatic System

Lymphadenopathy

Hypersensitivity

Rarely, angioedema

Nervous System

Febrile seizures

Skir

Sterile injection site abscess

DOSAGE AND ADMINISTRATION

Liquid PedvaxHIB

FOR INTRAMUSCULAR ADMINISTRATION

DO NOT INJECT INTRAVENOUSLY

If there is an interruption or delay between doses in the primary series, there is no need to repeat the series, but dosing should be continued at the next clinic visit. (See CONTRAINDICATIONS and PRECAUTIONS.)

2 to 14 Months of Age

Infants 2 to 14 months of age should receive a 0.5 mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5 mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see below and TABLE 6). Infants born prematurely, regardless of birth weight, should be vaccinated at the same chronological age and according to the same schedule and precautions as full-term infants and children.⁴⁶

15 Months of Age and Older

Children 15 months of age and older previously unvaccinated against Hib disease should receive a single 0.5 mL dose of vaccine.

Booster Dose

In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 to 15 months of age, but not earlier than 2 months after the second dose.

Vaccination regimens for Liquid PedvaxHIB by age group are outlined in TABLE 6.

| | TABLE 6 <u>Vaccination Regimens for Liquid PedvaxHIB</u> <u>By Age Groups</u> | |
|-------------------------------|---|---------------------------------|
| Age (Months) at First Dose | Primary | Age (Months) at Booster Dose |
| 2–10 11–14 | 2 doses, 2 mo. apart 2 doses, 2 mo. apart | 12–15 |
| 15–71 | 1 dose | _ |

Interchangeability

PedvaxHIB may be interchanged with other licensed Haemophilus b Conjugate Vaccines for the primary and booster doses.⁵² (See CLINICAL PHARMACOLOGY.) *Use with Other Vaccines*

Results from clinical studies indicate that Liquid PedvaxHIB can be administered concomitantly with DTP, OPV, eIPV (enhanced inactivated poliovirus vaccine), VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)], M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live) or RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)]. No impairment of immune response to these individually tested vaccine antigens was demonstrated.

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The type, frequency and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen with the other vaccines when given alone. (See CLINICAL PHARMACOLOGY.)

In addition, a PRP-OMPC-containing product, COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with a booster dose of DTaP [diphtheria, tetanus, acellular pertussis] at approximately 15 months of age, using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated. COMVAX has also been administered concomitantly with the primary series of DTaP to a limited number of infants. PRP antibody responses are satisfactory for COMVAX, but immune responses are currently unavailable for DTaP (see Manufacturer's Product Circular for COMVAX). No serious vaccine-related adverse events were reported.³³

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit.

Liquid PedvaxHIB is a slightly opaque white suspension. (See DESCRIPTION.)

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Inject 0.5 mL intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm. The buttocks should not be used for active vaccination of infants and children, because of the potential risk of injury to the sciatic nerve.

HOW SUPPLIED

Liquid PedvaxHIB is supplied as follows:

No. 4897 — A box of 10 single-dose vials of liquid vaccine, **NDC** 0006-4897-00. *Storage*

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE.

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EXHIBIT 241

Case 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 142 of 49 These highlights do not include all the information needed to use • The tip caps of the prefilled syringes contain natural rubber latex which ENGERIX-B safely and effectively. See full prescribing information for may cause allergic reactions. (5.1) ENGERIX-B. • Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Procedures should be in place to avoid ENGERIX-B [Hepatitis B Vaccine (Recombinant)] injectable suspension, falling injury and to restore cerebral perfusion following syncope. (5.2) for intramuscular use Temporarily defer vaccination of infants with a birth weight less than Initial U.S. Approval: 1989 2,000 g born to hepatitis B surface antigen (HBsAg)-negative mothers. (5.3) · Apnea following intramuscular vaccination has been observed in some -- INDICATIONS AND USAGE-infants born prematurely. Decisions about when to administer an ENGERIX-B is a vaccine indicated for immunization against infection caused intramuscular vaccine, including ENGERIX-B, to infants born prematurely by all known subtypes of hepatitis B virus. (1) should be based on consideration of the infant's medical status, and the ---DOSAGE AND ADMINISTRATION ----potential benefits and possible risks of vaccination. (5.4) For intramuscular administration. (2, 2.2) -- ADVERSE REACTIONS --• Persons from birth through 19 years of age: A series of 3 doses (0.5 mL The most common solicited adverse reactions were injection-site soreness each) on a 0-, 1-, 6-month schedule. (2.3) (22%) and fatigue (14%). (6.1) Persons 20 years of age and older: A series of 3 doses (1 mL each) on a 0-, 1-, 6-month schedule. (2.3) To report SUSPECTED ADVERSE REACTIONS, contact Adults on hemodialysis: A series of 4 doses (2 mL each) as a single 2-mL GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or dose or as two 1-mL doses on a 0-, 1-, 2-, 6-month schedule. (2.3) www.vaers.hhs.gov. --- DOSAGE FORMS AND STRENGTHS--- DRUG INTERACTIONS---ENGERIX-B is a sterile suspension available in the following presentations: Do not mix ENGERIX-B with any other vaccine or product in the same • 0.5-mL (10 mcg) single-dose vials and prefilled syringes (3) syringe or vial. (7.1) • 1-mL (20 mcg) single-dose vials and prefilled syringes (3) - USE IN SPECIFIC POPULATIONS

See 17 for PATIENT COUNSELING INFORMATION.

• Antibody responses are lower in persons older than 60 years than in

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FULL PRESCRIBING INFORMATION: CONTENTS*

-- CONTRAINDICATIONS --

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any

hepatitis B-containing vaccine, or to any component of ENGERIX-B,

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Preparation for Administration
 - 2.2 Administration
 - 2.3 Recommended Dose and Schedule
 - 2.4 Alternate Dosing Schedules
 - 2.5 Booster Vaccinations
 - 2.6 Known or Presumed Exposure to Hepatitis B Virus
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Latex

including yeast. (4)

- 5.2 Syncope
- 5.3 Infants Weighing Less than 2,000 g at Birth
- 5.4 Apnea in Premature Infants
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7 DRUG INTERACTIONS

vounger adults. (8.5)

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- *Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENGERIX-B is indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration. See Section 2.2 for subcutaneous administration in persons at risk of hemorrhage.

2.1 Preparation for Administration

Shake well before use. With thorough agitation, ENGERIX-B is a homogeneous, turbid white suspension. Do not administer if it appears otherwise. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

For the prefilled syringes, attach a sterile needle and administer intramuscularly.

For the vials, use a sterile needle and sterile syringe to withdraw the vaccine dose and administer intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated. Use a separate sterile needle and syringe for each individual.

2.2 Administration

ENGERIX-B should be administered by intramuscular injection. The preferred administration site is the anterolateral aspect of the thigh for infants younger than 1 year and the deltoid muscle in older children (whose deltoid is large enough for an intramuscular injection) and adults. ENGERIX-B should not be administered in the gluteal region; such injections may result in suboptimal response.

ENGERIX-B may be administered subcutaneously to persons at risk of hemorrhage (e.g., hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result in a lower antibody response. Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons who are at risk of hemorrhage with intramuscular injections.

Do not administer this product intravenously or intradermally.

2.3 Recommended Dose and Schedule

Persons from Birth through 19 Years

Primary immunization for infants (born of hepatitis B surface antigen [HBsAg]-negative or HBsAg-positive mothers), children (birth through 10 years), and adolescents (aged 11 through 19 years) consists of a series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule.

Persons Aged 20 Years and Older

Primary immunization for persons aged 20 years and older consists of a series of 3 doses (1 mL each) given on a 0-, 1-, and 6-month schedule.

Adults on Hemodialysis

Primary immunization consists of a series of 4 doses (2-mL each) given as a single 2-mL dose or two 1-mL doses on a 0-, 1-, 2-, and 6-month schedule. In hemodialysis patients, antibody response is lower than in healthy persons and protection may persist only as long as antibody levels remain above 10 mIU/mL. Therefore, the need for booster doses should be assessed by annual antibody testing. A 2-mL booster dose (as a single 2-mL dose or two 1-mL doses) should be given when antibody levels decline below 10 mIU/mL.

1 [See Clinical Studies (14.2).]

Table 1. Recommended Dosage and Administration Schedules

| Group | Dose ^a | Schedules |
|-------------------------------------|-------------------|-------------------|
| Infants born of: | | |
| HBsAg-negative mothers | 0.5 mL | 0, 1, 6 months |
| HBsAg-positive mothers ^b | 0.5 mL | 0, 1, 6 months |
| Children: | | |
| Birth through 10 years | 0.5 mL | 0, 1, 6 months |
| Adolescents: | | |
| Aged 11 through 19 years | 0.5 mL | 0, 1, 6 months |
| Adults: | | |
| Aged 20 years and older | 1 mL | 0, 1, 6 months |
| Adults on hemodialysis | 2 mL ^c | 0, 1, 2, 6 months |

HBsAg = Hepatitis B surface antigen.

2.4 Alternate Dosing Schedules

There are alternate dosing and administration schedules which may be used for specific populations (e.g., neonates born of hepatitis B–infected mothers, persons who have or might have been recently exposed to the virus, and travelers to high-risk areas) (Table 2). For some of these alternate schedules, an additional dose at 12 months is recommended for prolonged maintenance of protective titers.

^a 0.5 mL (10 mcg); 1 mL (20 mcg).

^b Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth [see Dosage and Administration (2.6)].

^c Given as a single 2-mL dose or as two 1-mL doses.

Table 2. Alternate Dosage and Administration Schedules

| Group | Dose ^a | Schedules |
|-------------------------------------|-------------------|-------------------------------|
| Infants born of: | | |
| HBsAg-positive mothers ^b | 0.5 mL | 0, 1, 2, 12 months |
| Children: | | |
| Birth through 10 years | 0.5 mL | 0, 1, 2, 12 months |
| Aged 5 through 10 years | 0.5 mL | 0, 12, 24 months ^c |
| Adolescents: | | |
| Aged 11 through 16 years | 0.5 mL | 0, 12, 24 months ^c |
| Aged 11 through 19 years | 1 mL | 0, 1, 6 months |
| Aged 11 through 19 years | 1 mL | 0, 1, 2, 12 months |
| Adults: | | |
| Aged 20 years and older | 1 mL | 0, 1, 2, 12 months |

HBsAg = Hepatitis B surface antigen.

2.5 Booster Vaccinations

Whenever administration of a booster dose is appropriate, the dose of ENGERIX-B is 0.5 mL for children aged 10 years and younger and 1 mL for persons aged 11 years and older. Studies have demonstrated a substantial increase in antibody titers after booster vaccination with ENGERIX-B. See Section 2.3 for information on booster vaccination for adults on hemodialysis.

2.6 Known or Presumed Exposure to Hepatitis B Virus

Persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers, persons who experienced percutaneous or permucosal exposure to the virus) should be given hepatitis B immune globulin (HBIG) in addition to ENGERIX-B in accordance with Advisory Committee on Immunization Practices recommendations and with the package insert for HBIG. ENGERIX-B can be given on either dosing schedule (0, 1, and 6 months or 0, 1, 2, and 12 months).

3 DOSAGE FORMS AND STRENGTHS

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled TIP-LOK syringes
- 1-mL (20 mcg) single-dose vials and prefilled TIP-LOK syringes

[See Description (11), How Supplied/Storage and Handling (16).]

^a 0.5 mL (10 mcg); 1 mL (20 mcg).

^b Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12 hours after birth [see Dosage and Administration (2.6)].

^c For children and adolescents for whom an extended administration schedule is acceptable based on risk of exposure.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast, is a contraindication to administration of ENGERIX-B [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Infants Weighing Less than 2,000 g at Birth

Hepatitis B vaccine should be deferred for infants with a birth weight <2,000 g if the mother is documented to be HBsAg negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or hospital discharge. Infants born weighing <2,000 g to HBsAgpositive mothers should receive vaccine and HBIG within 12 hours after birth. Infants born weighing <2,000 g to mothers of unknown HBsAg status should receive vaccine and HBIG within 12 hours after birth if the mother's HBsAg status cannot be determined within the first 12 hours of life. The birth dose in infants born weighing <2,000 g should not be counted as the first dose in the vaccine series and it should be followed with a full 3-dose standard regimen (total of 4 doses).² [See Dosage and Administration (2).]

5.4 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. For ENGERIX-B, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born of mothers who are HBsAg positive if vaccination is delayed.

5.5 Preventing and Managing Allergic Vaccine Reactions

Prior to immunization, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of

immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur. [See Contraindications (4).]

5.6 Moderate or Severe Acute Illness

To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine adverse effects, vaccination with ENGERIX-B should be postponed in persons with moderate or severe acute febrile illness unless they are at immediate risk of hepatitis B infection (e.g., infants born of HBsAg-positive mothers).

5.7 Altered Immunocompetence

Immunocompromised persons may have a diminished immune response to ENGERIX-B, including individuals receiving immunosuppressant therapy.

5.8 Multiple Sclerosis

Results from 2 clinical studies indicate that there is no association between hepatitis B vaccination and the development of multiple sclerosis,³ and that vaccination with hepatitis B vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.⁴

5.9 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. ENGERIX-B may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The most common solicited adverse reactions were injection site soreness (22%) and fatigue (14%).

In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy adults and children who were initially seronegative for hepatitis B markers, and healthy neonates. All subjects were monitored for 4 days post-administration. Frequency of adverse reactions tended to decrease with successive doses of ENGERIX-B.

Using a symptom checklist, the most frequently reported adverse reactions were injection site soreness (22%) and fatigue (14%). Other reactions are listed below. Parent or guardian completed forms for children and neonates. Neonatal checklist did not include headache, fatigue, or dizziness.

<u>Incidence 1% to 10% of Injections</u>

Nervous System Disorders: Dizziness, headache.

General Disorders and Administration Site Conditions: Fever (>37.5°C), injection site erythema, injection site induration, injection site swelling.

<u>Incidence <1% of Injections</u>

Infections and Infestations: Upper respiratory tract illnesses.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Agitation, insomnia.

Nervous System Disorders: Somnolence, tingling.

Vascular Disorders: Flushing, hypotension.

Gastrointestinal Disorders: Abdominal pain/cramps, constipation, diarrhea, nausea, vomiting.

Skin and Subcutaneous Tissue Disorders: Erythema, petechiae, pruritus, rash, sweating, urticaria.

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, myalgia, pain/stiffness in arm, shoulder, or neck.

General Disorders and Administration Site Conditions: Chills, influenza-like symptoms, injection site ecchymosis, injection site pain, injection site pruritus, irritability, malaise, weakness.

In a clinical trial, 416 adults with type 2 diabetes and 258 control subjects without type 2 diabetes who were seronegative for hepatitis B markers received at least 1 dose of ENGERIX-B. Subjects were monitored for solicited adverse reactions for 4 days following each vaccination. The most frequently reported solicited adverse reactions in the entire study population were injection site pain (reported in 39% of diabetic subjects and 45% of control subjects) and fatigue (reported in 29% of diabetic subjects and 27% of control subjects). Serious adverse events were monitored through 30 days following the last vaccination. Serious adverse events (SAEs) occurred in 3.8% of diabetic subjects and 1.6% of controls. No SAEs were deemed related to ENGERIX-B.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ENGERIX-B. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Infections and Infestations

Herpes zoster, meningitis.

Blood and Lymphatic System Disorders

Thrombocytopenia.

<u>Immune System Disorders</u>

Allergic reaction, anaphylactoid reaction, anaphylaxis. An apparent hypersensitivity syndrome (serum sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses, and erythema nodosum.

Nervous System Disorders

Encephalitis; encephalopathy; migraine; multiple sclerosis; neuritis; neuropathy including hypoesthesia, paresthesia, Guillain-Barré syndrome and Bell's palsy; optic neuritis; paralysis; paresis; seizures; syncope; transverse myelitis.

Eye Disorders

Conjunctivitis, keratitis, visual disturbances.

Ear and Labyrinth Disorders

Earache, tinnitus, vertigo.

Cardiac Disorders

Palpitations, tachycardia.

Vascular Disorders

Vasculitis.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, bronchospasm including asthma-like symptoms.

Gastrointestinal Disorders

Dyspepsia.

Skin and Subcutaneous Tissue Disorders

Alopecia, angioedema, eczema, erythema multiforme including Stevens-Johnson syndrome, erythema nodosum, lichen planus, purpura.

Musculoskeletal and Connective Tissue Disorders

Arthritis, muscular weakness.

General Disorders and Administration Site Conditions

Injection site reaction.

Investigations

Abnormal liver function tests.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Vaccines and Immune Globulin

ENGERIX-B may be administered concomitantly with immune globulin.

When concomitant administration of other vaccines or immune globulin is required, they should be given with different syringes and at different injection sites. Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial.

7.2 Interference with Laboratory Tests

HBsAg derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of a hepatitis B vaccine, including ENGERIX-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies of ENGERIX-B in pregnant women in the U.S. Available data do not suggest an increased risk of major birth defects and miscarriage in women who received ENGERIX-B during pregnancy (see Data).

There are no animal studies with ENGERIX-B to inform use during pregnancy. A developmental toxicity study was performed in female rats administered a vaccine with the same hepatitis B surface antigen component and quantity as ENGERIX-B prior to mating and during gestation (0.2 mL at each occasion). This study revealed no adverse effects on fetal or pre-weaning development (*see Data*).

Data

Human Data: In an evaluation of pre- and post-licensure clinical trials of ENGERIX-B, 58 pregnant women were inadvertently administered ENGERIX-B following their last menstrual period. After excluding elective terminations (n = 6), those with an unknown outcome (n = 3), those with exposure in the third trimester (n = 1), and those with an unknown exposure timing

(n = 22), there were 26 pregnancies with known outcomes with exposure in the first or second trimester. Miscarriage was reported in 11.5% of pregnancies with exposure prior to 20 weeks of gestation (3/26) and major birth defects were reported in 0% (0/23) of live births born to women with exposure during the first or second trimester. The rates of miscarriage and major birth defects were consistent with estimated background rates.

No pregnancy registry for ENGERIX-B was conducted. TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine] is a bivalent vaccine containing the same hepatitis B surface antigen component and quantity as used in ENGERIX-B. Therefore, clinical data accrued with TWINRIX are relevant to ENGERIX-B. A pregnancy exposure registry was maintained for TWINRIX from 2001 to 2015. The registry prospectively enrolled 245 women who received a dose of TWINRIX during pregnancy or within 28 days prior to conception. After excluding induced abortions (n = 6, including one of a fetus with congenital anomalies), those lost to follow-up (n = 142), those with exposure in the third trimester (n = 1), and those with an unknown exposure timing (n = 9), there were 87 pregnancies with known outcomes with exposure within 28 days prior to conception, or in the first or second trimesters. Miscarriage was reported for 9.6% of pregnancies with exposure to TWINRIX prior to 20 weeks gestation (8/83). Major birth defects were reported for 3.8% of live born infants whose mothers were exposed within 28 days prior to conception or during the first or second trimester (3/80). The rates of miscarriage and major birth defects were consistent with estimated background rates.

Animal Data: In a developmental toxicity study, female rats were administered TWINRIX, which contains the same hepatitis B surface antigen component and quantity as ENGERIX-B, by intramuscular injection on Day 30 prior to mating and on gestation Days 6, 8, 11, and 15. The total dose was 0.2 mL (divided) at each occasion (a single human dose is 1 mL). No adverse effects on pre-weaning development up to post-natal Day 25 were observed. There were no fetal malformations or variations.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ENGERIX-B in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENGERIX-B and any potential adverse effects on the breastfed child from ENGERIX-B or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of ENGERIX-B have been established in all pediatric age-groups. Maternally transferred antibodies do not interfere with the active immune response to the vaccine. [See Adverse Reactions (6), Clinical Studies (14.1, 14.3, 14.4).]

The timing of the first dose in infants weighing less than 2,000 g at birth depends on the HBsAg status of the mother. [See Warnings and Precautions (5.3).]

8.5 Geriatric Use

Clinical studies of ENGERIX-B used for licensure did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. However, in later studies it has been shown that a diminished antibody response and seroprotective levels can be expected in persons older than 60 years.⁵ [See Clinical Studies (14.2).]

11 DESCRIPTION

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] is a sterile suspension of noninfectious HBsAg for intramuscular administration. It contains purified surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The HBsAg expressed in the cells is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture ENGERIX-B result in a product that contains no more than 5% yeast protein.

Each 0.5-mL pediatric/adolescent dose contains 10 mcg of HBsAg adsorbed on 0.25 mg aluminum as aluminum hydroxide.

Each 1-mL adult dose contains 20 mcg of HBsAg adsorbed on 0.5 mg aluminum as aluminum hydroxide.

ENGERIX-B contains the following excipients: Sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).

ENGERIX-B is available in vials and prefilled syringes. The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

ENGERIX-B is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

Antibody concentrations ≥ 10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.¹ Seroconversion is defined as antibody titers ≥ 1 mIU/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ENGERIX-B has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Vaccination of female rats with TWINRIX, which contains the same HBsAg component and quantity as ENGERIX-B, had no effect on fertility. [See Use in Specific Populations (8.1).]

14 CLINICAL STUDIES

14.1 Efficacy in Neonates

Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection. ^{6,7} Fifty-eight neonates born of mothers who were both HBsAgpositive and hepatitis B "e" antigen (HBeAg)-positive were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 2 months, without concomitant hepatitis B immune globulin (HBIG). Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

14.2 Efficacy and Immunogenicity in Specific Populations

Homosexual Men

ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months was evaluated in homosexual men aged 16 to 59 years. Four of 244 subjects became infected with hepatitis B during the period prior to completion of the 3-dose immunization schedule. No additional subjects became infected during the 18-month follow-up period after completion of the immunization course.

Adults with Chronic Hepatitis C

In a clinical trial of 67 adults aged 25 to 67 years with chronic hepatitis C, ENGERIX-B (20 mcg/1 mL) was given at 0, 1, and 6 months. Of the subjects assessed at Month 7 (n = 31), 100% responded with seroprotective titers. The geometric mean antibody titer (GMT) was 1,260 mIU/mL (95% Confidence Interval [CI]: 709, 2,237).

Adults on Hemodialysis

Hemodialysis patients given hepatitis B vaccines respond with lower titers, which remain at protective levels for shorter durations than in normal subjects. In a clinical trial of 56 adults who had been on hemodialysis for a mean period of 56 months, ENGERIX-B (40 mcg/2 mL given as two 1-mL doses) was given at 0, 1, 2, and 6 months. Two months after the fourth dose, 67% (29/43) of patients had seroprotective antibody levels (≥10 mIU/mL) and the GMT among seroconverters was 93 mIU/mL.

Adults with Type 2 Diabetes Mellitus

In a descriptive study, 674 adult subjects with type 2 diabetes (diagnosed within the preceding 5 years) or without type 2 diabetes were enrolled and stratified by age and body mass index (BMI). The per-protocol immunogenicity cohort included 378 diabetic subjects and 189 matched control subjects who received ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months. Among these subjects, the mean age was 54 years (range: 20 to 82 years); mean BMI was 32 kg/m² (range: 17 to 64 kg/m²); 51% were male; 88% were white, 3% were American Indian or Alaskan Native, 3% were black, 2% were Asian, 4% were other racial groups; 2% were Hispanic or Latino.

The overall seroprotection rates (1 month after the third dose) were 75% (95% CI: 71, 80) in patients with diabetes and 82% (95% CI: 76, 87) in control subjects. The seroprotection rates in those with diabetes aged 20 to 39 years, 40 to 49 years, 50 to 59 years, and at least 60 years were 89%, 81%, 83%, and 58%, respectively. The seroprotection rates in those without diabetes in these same age-groups were 100%, 86%, 82%, and 70%, respectively. Subjects with diabetes and a BMI of at least 30 kg/m² had a seroprotection rate of 72% compared with 80% in diabetic subjects with lower BMIs. In control subjects, seroprotection rates were 82% in those with a BMI of at least 30 kg/m² and 83% in those with lower BMIs.

14.3 Immunogenicity in Neonates

In clinical studies, neonates were given ENGERIX-B (10 mcg/0.5 mL) at age 0, 1, and 6 months or at age 0, 1, and 2 months. The immune response to vaccination was evaluated in sera obtained 1 month after the third dose of ENGERIX-B.

Among infants administered ENGERIX-B at age 0, 1, and 6 months, 100% of evaluable subjects (n = 52) seroconverted by Month 7. The GMT was 713 mIU/mL. Of these, 97% had seroprotective levels (\geq 10 mIU/mL).

Among infants enrolled (n = 381) to receive ENGERIX-B at age 0, 1, and 2 months, 96% had seroprotective levels (\geq 10 mIU/mL) by Month 4. The GMT among seroconverters (n = 311) (antibody titer \geq 1 mIU/mL) was 210 mIU/mL. A subset of these children received a fourth dose of ENGERIX-B at age 12 months. One month following this dose, seroconverters (n = 126) had a GMT of 2,941 mIU/mL.

14.4 Immunogenicity in Children and Adults

Persons Aged 6 Months through 10 Years

In clinical trials, children (N = 242) aged 6 months through 10 years were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 6 months. One to 2 months after the third dose, the seroprotection rate was 98% and the GMT of seroconverters was 4,023 mIU/mL.

Persons Aged 5 through 16 Years

In a separate clinical trial including both children and adolescents aged 5 through 16 years, ENGERIX-B (10 mcg/0.5 mL) was administered at 0, 1, and 6 months (n = 181) or 0, 12, and

24 months (n = 161). Immediately before the third dose of vaccine, seroprotection was achieved in 92.3% of subjects vaccinated on the 0-, 1-, and 6-month schedule and 88.8% of subjects on the 0-, 12-, and 24-month schedule (GMT: 118 mIU/mL versus 162 mIU/mL, respectively, P = 0.18). One month following the third dose, seroprotection was achieved in 99.5% of children vaccinated on the 0-, 1-, and 6-month schedule compared with 98.1% of those on the 0-, 12-, and 24-month schedule. GMTs were higher (P = 0.02) for children receiving vaccine on the 0-, 1-, and 6-month schedule compared with those on the 0-, 12-, and 24-month schedule (5,687 mIU/mL versus 3,159 mIU/mL, respectively).

Persons Aged 11 through 19 Years

In clinical trials with healthy adolescent subjects aged 11 through 19 years, ENGERIX-B (10 mcg/0.5 mL) given at 0, 1, and 6 months produced a seroprotection rate of 97% at Month 8 (n = 119) with a GMT of 1,989 mIU/mL (n = 118, 95% CI: 1,318, 3,020). Immunization with ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months produced a seroprotection rate of 99% at Month 8 (n = 122) with a GMT of 7,672 mIU/mL (n = 122, 95% CI: 5,248, 10,965).

Persons Aged 16 through 65 Years

Clinical trials in healthy adult and adolescent subjects (aged 16 through 65 years) have shown that following a course of 3 doses of ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months, the seroprotection (antibody titers \geq 10 mIU/mL) rate for all individuals was 79% at Month 6 (5 months after second dose) and 96% at Month 7 (1 month after third dose); the GMT for seroconverters was 2,204 mIU/mL at Month 7 (n = 110).

An alternate 3-dose schedule (20 mcg/1 mL given at 0, 1, and 2 months) designed for certain populations (e.g., individuals who have or might have been recently exposed to the virus and travelers to high-risk areas) was also evaluated. At Month 3 (1 month after third dose), 99% of all individuals were seroprotected and remained protected through Month 12. On the alternate schedule, a fourth dose of ENGERIX-B (20 mcg/1 mL) at 12 months produced a GMT of 9,163 mIU/mL at Month 13 (1 month after fourth dose) (n = 373).

Persons Aged 40 Years and Older

Among subjects aged 40 years and older given ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months, the seroprotection rate 1 month after the third dose was 88% and the GMT for seroconverters was 610 mIU/mL (n = 50). In adults aged older than 40 years, ENGERIX-B produced anti-HBsAg antibody titers that were lower than those in younger adults.

14.5 Interchangeability with Other Hepatitis B Vaccines

A controlled study (N = 48) demonstrated that completion of a course of immunization with 1 dose of ENGERIX-B (20 mcg/1 mL) at Month 6 following 2 doses of RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant)] (10 mcg) at Months 0 and 1 produced a similar GMT (4,077 mIU/mL) to immunization with 3 doses of RECOMBIVAX HB (10 mcg) at Months 0, 1,

and 6 (GMT: 2,654 mIU/mL). Thus, ENGERIX-B can be used to complete a vaccination course initiated with RECOMBIVAX HB.⁸

15 REFERENCES

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- 6. André FE, Safary A. Clinical experience with a yeast-derived hepatitis B vaccine. In: Zuckerman AJ, ed. *Viral Hepatitis and Liver Disease*. New York, NY: Alan R Liss, Inc.; 1988:1025-1030.
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16 HOW SUPPLIED/STORAGE AND HANDLING

ENGERIX-B is available in single-dose vials and prefilled disposable TIP-LOK syringes (packaged without needles) (Preservative-Free Formulation):

10 mcg/0.5 mL Pediatric/Adolescent Dose

NDC 58160-820-01 Vial in Package of 10: NDC 58160-820-11

NDC 58160-820-43 Syringe in Package of 10: NDC 58160-820-52

20 mcg/mL Adult Dose

NDC 58160-821-01 Vial in Package of 10: NDC 58160-821-11

NDC 58160-821-05 Syringe in Package of 1: NDC 58160-821-34

NDC 58160-821-43 Syringe in Package of 10: NDC 58160-821-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been frozen. Do not dilute to administer.

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients and parents or guardians of the potential benefits and risks of immunization with ENGERIX-B.
- Emphasize, when educating vaccine recipients and parents or guardians regarding potential side effects, that ENGERIX-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Instruct vaccine recipients and parents or guardians to report any adverse events to their healthcare provider.
- Give vaccine recipients and parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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ENG:XXPI

EXHIBIT 242

Case 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 159 of 497 mL (40 mcg) single-dose vials (3, 11, 16.1)

These highlights do not include all the information needed to use RECOMBIVAX HB safely and effectively. See full prescribing information for RECOMBIVAX HB.

RECOMBIVAX HB® Hepatitis B Vaccine (Recombinant) Suspension for intramuscular injection Initial U.S. Approval: 1986

-----RECENT MAJOR CHANGES -----Dosage and Administration (2) 12/2018

-----INDICATIONS AND USAGE -----

RECOMBIVAX HB is a vaccine indicated for prevention of infection caused by all known subtypes of hepatitis B virus. RECOMBIVAX HB is approved for use in individuals of all ages. RECOMBIVAX HB Dialysis Formulation is approved for use in predialysis and dialysis patients 18 years of age and older. (1)

- Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule. (2.1)
- Adolescents 11 through 15 years of age: A series of either 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule or a series of 2 doses (1.0 mL) on a 0- and 4- to 6-month schedule).
- Persons 20 years of age and older: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule. (2.1)

RECOMBIVAX HB Dialysis Formulation

Adults on predialysis or dialysis: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule. (2.1)

---- DOSAGE FORMS AND STRENGTHS ------

RECOMBIVAX HB is a sterile suspension available in the following presentations:

- 0.5 mL (5 mcg) Pediatric/Adolescent Formulation single-dose vials and prefilled syringes (3, 11, 16.1)
- 1 mL (10 mcg) Adult Formulation single-dose vials and prefilled syringes (3, 11, 16.1)

RECOMBIVAX HB Dialysis Formulation is a sterile suspension available in the following presentation:

-----CONTRAINDICATIONS -----

Severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of RECOMBIVAX HB, including yeast. (4, 11)

---- WARNINGS AND PRECAUTIONS ---

The vial stopper, the syringe plunger stopper, and tip cap contain dry natural latex rubber which may cause allergic reactions in latex-sensitive individuals. (5.1)

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including RECOMBIVAX HB, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.2)

---- ADVERSE REACTIONS ----

In healthy infants and children (up to 10 years of age), the most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, fever, diarrhea, fatigue/weakness, diminished appetite, and rhinitis. (6.1)

In healthy adults, injection site reactions and systemic adverse reactions were reported following 17% and 15% of the injections, respectively. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

------DRUG INTERACTIONS ------

Do not mix RECOMBIVAX HB with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RECOMBIVAX HB® [Hepatitis B Vaccine, Recombinant] is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. RECOMBIVAX HB is approved for use in individuals of all

ages. RECOMBIVAX HB Dialysis Formulation is approved for use in adult predialysis and dialysis patients 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration. See Section 2.2 for subcutaneous administration in persons with hemophilia.

RECOMBIVAX HB should be administered as soon as possible after being removed from refrigeration [see How Supplied/Storage and Handling (16)].

2.1 Dosage and Schedule

RECOMBIVAX HB:

Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule.

Adolescents 11 through 15 years of age: A series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month schedule or a series of 2 doses (1.0 mL each) on a 0- and 4- to 6-month schedule.

Persons 20 years of age and older: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule.

RECOMBIVAX HB Dialysis Formulation:

Adults on predialysis and dialysis: A series of 3 doses (1.0 mL each) given on a 0-, 1-, and 6-month schedule.

Table 1 summarizes the dose and formulation of RECOMBIVAX HB for specific populations, regardless of the risk of infection with hepatitis B virus.

Table 1: RECOMBIVAX HB Recommended Dose and Administration Schedules

| Group | Dose/Regimen |
|---|--|
| Infants*, Children and Adolescents 0-19 years of age (Pediatric/Adolescent Formulation) | 5 mcg (0.5 mL) 3 doses at 0, 1, and 6 months |
| Adolescents [†] 11 through 15 years of age (Adult formulation) | 10 mcg [‡] (1.0 mL) 2 doses at 0 and 4-6 months |
| Adults ≥20 years of age (Adult formulation) | 10 mcg [‡] (1.0 mL) 3 doses at 0, 1, and 6 months |
| Predialysis and Dialysis Patients [§] (Dialysis formulation) | 40 mcg (1.0 mL) 3 doses at 0, 1, and 6 months |

^{*} For specific recommendations for infants see ACIP recommendations. {1}

2.2 Preparation and Administration

Shake the single-dose vial or single-dose prefilled syringe well to obtain a slightly opaque, white suspension before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the suspension does not appear homogeneous or if extraneous particulate matter remains or if discoloration is observed.

For single-dose vials, withdraw and administer entire dose of RECOMBIVAX HB intramuscularly using a sterile needle and syringe.

For single-dose prefilled syringes, securely attach a needle by twisting in a clockwise direction and administer dose of RECOMBIVAX HB intramuscularly.

[†] Adolescents (11 through 15 years of age) may receive either regimen: 3 x 5 mcg (Pediatric Formulation) or 2 x 10 mcg (Adult Formulation).

If the suggested dose (10 mcg) is not available, the appropriate dosage can be achieved with two 5 mcg doses. However, the Dialysis Formulation may be used only for adult predialysis/dialysis patients.

[§] See also recommendations for revaccination of predialysis and dialysis patients in [Dosage and Administration (2.4)].

The deltoid muscle is the preferred site for intramuscular injection for adults, adolescents and children 1 year of age and older whose deltoid is large enough for intramuscular injection. The anterolateral aspect of the thigh is the preferred site for intramuscular injection for infants younger than 1 year of age. RECOMBIVAX HB should not be administered in the gluteal region, as injections given in the buttocks have resulted in lower seroconversion rates than expected. {2}

RECOMBIVAX HB may be administered subcutaneously to persons at risk for hemorrhage following intramuscular injections (e.g., hemophiliacs). However, hepatitis B vaccines are known to result in lower antibody response when administered subcutaneously.{3} Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, consider subcutaneous administration only in persons who are at risk of hemorrhage following intramuscular injections.

Do not administer intravenously or intradermally.

2.3 Known or Presumed Exposure to Hepatitis B Virus

Known or Presumed Exposure to HBsAg

Refer to recommendations of the Advisory Committee on Immunization Practices (ACIP) and to the package insert for hepatitis B immune globulin (HBIG) for management of persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers or persons who experienced percutaneous or permucosal exposure to the virus). When recommended, administer RECOMBIVAX HB and HBIG intramuscularly at separate sites (e.g., opposite anterolateral thighs for exposed neonates) as soon as possible after exposure. Administer additional doses of RECOMBIVAX HB (to complete a vaccination series) in accordance with ACIP recommendations.

2.4 Booster Vaccinations

The duration of the protective effect of RECOMBIVAX HB in healthy vaccinees is unknown at present and the need for booster doses is not yet defined. The ACIP provides recommendations for use of a booster dose or revaccination series in previously vaccinated individuals with known or presumed exposure to Hepatitis B Virus.

Consider a booster dose or revaccination with RECOMBIVAX HB Dialysis Formulation (blue color code) in predialysis/dialysis patients if the anti-HBs level is less than 10 mIU/mL at 1 to 2 months after the third dose. Assess the need for a booster dose annually by antibody testing, and give a booster dose when the anti-HBs level declines to less than 10 mIU/mL.{3}

3 DOSAGE FORMS AND STRENGTHS

RECOMBIVAX HB is a sterile suspension available in the following presentations:

- 0.5 mL (5 mcg) Pediatric/Adolescent Formulation single-dose vials and prefilled syringes
- 1 mL (10 mcg) Adult Formulation single-dose vials and prefilled syringes RECOMBIVAX HB DIALYSIS FORMULATION is a sterile suspension available in the following presentation:
- 1 mL (40 mcg) single-dose vial [see Description (11) and How Supplied/Storage and Handling (16)]

4 CONTRAINDICATIONS

Do not administer RECOMBIVAX HB to individuals with a history of severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine or to any component of RECOMBIVAX HB, including yeast [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity to Latex

The vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber, which may cause allergic reactions in latex-sensitive individuals.

5.2 Apnea in Premature Infants

Apries following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including RECOMBIVAX HB, to infants born prematurely should be based on consideration of the individual infant's medical status and the

potential benefits and possible risks of vaccination. For RECOMBIVAX HB, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born to mothers who are HBsAg positive if vaccination is delayed.

5.3 Infants Weighing Less Than 2000 g

Hepatitis B vaccination should be delayed until 1 month of age or hospital discharge in infants weighing <2000 g if the mother is documented to be HBsAg negative at the time of the infant's birth. Infants weighing <2000 g born to HBsAg positive or HBsAg unknown mothers should receive vaccine and hepatitis B immune globulin (HBIG) in accordance with ACIP recommendations if HBsAg status cannot be determined [3] [see Dosage and Administration (2)].

5.4 Prevention and Management of Allergic Vaccine Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration [see Contraindications (4)].

5.5 Limitations of Vaccine Effectiveness

Hepatitis B virus has a long incubation period. RECOMBIVAX HB may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccination. Additionally, vaccination with RECOMBIVAX HB may not protect all individuals.

6 ADVERSE REACTIONS

In healthy infants and children (up to 10 years of age), the most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, fever, diarrhea, fatigue/weakness, diminished appetite, and rhinitis. In healthy adults, injection site reactions and systemic adverse reactions were reported following 17% and 15% of the injections, respectively.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

In three clinical studies, 434 doses of RECOMBIVAX HB, 5 mcg, were administered to 147 healthy infants and children (up to 10 years of age) who were monitored for 5 days after each dose. Injection site reactions and systemic adverse reactions were reported following 0.2% and 10.4% of the injections, respectively. The most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, fever (≥101°F oral equivalent), diarrhea, fatigue/weakness, diminished appetite, and rhinitis.

In a study that compared the three-dose regimen (5 mcg) with the two-dose regimen (10 mcg) of RECOMBIVAX HB in adolescents, the overall frequency of adverse reactions was generally similar.

In a group of studies, 3258 doses of RECOMBIVAX HB, 10 mcg, were administered to 1252 healthy adults who were monitored for 5 days after each dose. Injection site reactions and systemic adverse reactions were reported following 17% and 15% of the injections, respectively. The following adverse reactions were reported:

Incidence Equal To or Greater Than 1% of Injections

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Injection site reactions consisting principally of soreness, and including pain, tenderness, pruritus, erythema, ecchymosis, swelling, warmth, nodule formation.

The most frequent systemic complaints include fatigue/weakness; headache; fever (≥100°F); malaise. GASTROINTESTINAL DISORDERS

Nausea; diarrhea

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Pharyngitis; upper respiratory infection

Incidence Less Than 1% of Injections

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS

Sweating; achiness; sensation of warmth; lightheadedness; chills; flushing

GASTROINTESTINAL DISORDERS

Vomiting; abdominal pains/cramps; dyspepsia; diminished appetite

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

Rhinitis; influenza; cough

NERVOUS SYSTEM DISORDERS

Vertigo/dizziness; paresthesia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Pruritus; rash (non-specified); angioedema; urticaria

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

Arthralgia including monoarticular; myalgia; back pain; neck pain; shoulder pain; neck stiffness

BLOOD AND LYMPHATIC DISORDERS

Lymphadenopathy

PSYCHIATRIC DISORDERS

Insomnia/disturbed sleep

EAR AND LABYRINTH DISORDERS

Earache

RENAL AND URINARY DISORDERS

Dysuria

CARDIAC DISORDERS

Hypotension

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported with use of the marketed vaccine. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to a vaccine exposure.

Immune System Disorders

Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria have been reported within the first few hours after vaccination. An apparent hypersensitivity syndrome (serum-sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses and erythema nodosum [see Warnings and Precautions (5.1)]. Autoimmune diseases including systemic lupus erythematosus (SLE), lupus-like syndrome, vasculitis, and polyarteritis nodosa have also been reported.

Gastrointestinal Disorders

Elevation of liver enzymes; constipation

Nervous System Disorders

Guillain-Barré syndrome; multiple sclerosis; exacerbation of multiple sclerosis; myelitis including transverse myelitis; seizure; febrile seizure; peripheral neuropathy including Bell's Palsy; radiculopathy; herpes zoster; migraine; muscle weakness; hypesthesia; encephalitis

Skin and Subcutaneous Disorders

Stevens-Johnson syndrome; alopecia; petechiae; eczema

Musculoskeletal and Connective Tissue Disorders

Arthritis

Pain in extremity

Blood and Lymphatic System Disorders

Increased erythrocyte sedimentation rate; thrombocytopenia

Psychiatric Disorders

Irritability; agitation; somnolence

Eye Disorders

Optic neuritis; tinnitus; conjunctivitis; visual disturbances; uveitis

Cardiac Disorders

Syncope; tachycardia

The following adverse reaction has been reported with another Hepatitis B Vaccine (Recombinant) but not with RECOMBIVAX HB: keratitis.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

Do not mix RECOMBIVAX HB with any other vaccine in the same syringe or vial. Use separate injection sites and syringes for each vaccine.

In clinical trials in children, RECOMBIVAX HB was concomitantly administered with one or more of the following US licensed vaccines: Diphtheria, Tetanus and whole cell Pertussis; oral Poliomyelitis vaccine; Measles, Mumps, and Rubella Virus Vaccine, Live; Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] or a booster dose of Diphtheria, Tetanus, acellular Pertussis. Safety and immunogenicity were similar for concomitantly administered vaccines compared to separately administered vaccines.

In another clinical trial, a related HBsAg-containing product, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combination product (no longer licensed), was given concomitantly with eIPV (enhanced inactivated Poliovirus vaccine) or VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], using separate sites and syringes for injectable vaccines. No serious vaccine-related adverse events were reported, and no impairment of immune response to these individually tested vaccine antigens was demonstrated.

The Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) combination product (no longer licensed) has also been administered concomitantly with the primary series of DTaP to a limited number of infants. No serious vaccine-related adverse events were reported.

7.2 Concomitant Administration with Immune Globulin

RECOMBIVAX HB may be administered concomitantly with HBIG. The first dose of RECOMBIVAX HB may be given at the same time as HBIG, but the injections should be administered at different sites.

7.3 Interference with Laboratory Tests

Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of a hepatitis B vaccine, including RECOMBIVAX HB.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

There are no adequate and well-controlled studies designed to evaluate RECOMBIVAX HB in pregnant women. Available post-approval data do not suggest an increased risk of miscarriage or major birth defects in women who received RECOMBIVAX HB during pregnancy.

Developmental toxicity studies have not been conducted with the vaccine in animals.

Data

Human Data

In post-licensure clinical studies of RECOMBIVAX HB, 26 pregnant women were inadvertently administered RECOMBIVAX HB following their last menstrual period. Among these pregnancies, after excluding elective terminations (n=3), there were 23 pregnancies with known outcomes all with exposure in the first trimester. Miscarriage was reported in 4 of 23 (17%) pregnancies and major birth defects were reported in 0 of 19 (0%) live births. The rates of miscarriage and major birth defects were consistent with estimated background rates.

Post-approval adverse reactions are reported voluntarily from a population of uncertain size. It is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

In prospectively reported spontaneous post-approval reports from 1986 to 2018, 105 women with known pregnancy outcomes were exposed to RECOMBIVAX HB during pregnancy following the last menstrual period. After excluding induced abortions (n=5), those with exposure in the third trimester (n=4), and those with an unknown exposure timing (n=6), there were 90 pregnancies with known outcomes with exposures in the first or second trimester. Miscarriage was reported for 7 of 90 (7.8%) pregnancies. Major birth defects were reported for 2 of 83 (2.4%) live born infants. The rates of miscarriage and major birth defects were consistent with estimated background rates.

8.2 Lactation

Risk Summary

It is not known whether RECOMBIVAX HB is excreted in human milk. Data are not available to assess the effects of RECOMBIVAX HB on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RECOMBIVAX HB and any potential adverse effects on the breastfed child from RECOMBIVAX HB or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to the disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of RECOMBIVAX HB have been established in all pediatric age groups. Maternally transferred antibodies do not interfere with the active immune response to the vaccine. [See Adverse Reactions (6.1) and Clinical Studies (14.1 and 14.2).] The safety and effectiveness of RECOMBIVAX HB Dialysis Formulation in children have not been established.

8.5 Geriatric Use

Clinical studies of RECOMBIVAX HB used for licensure did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. However, in later studies it has been shown that a diminished antibody response can be expected in persons older than 60 years of age.

11 DESCRIPTION

RECOMBIVAX HB Hepatitis B Vaccine (Recombinant) is a sterile suspension of non-infectious subunit viral vaccine derived from HBsAg produced in yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories.

The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The fermentation process involves growth of *Saccharomyces cerevisiae* on a complex fermentation medium which consists of an extract of yeast, soy peptone, dextrose, amino acids and mineral salts. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The purified protein is treated in phosphate buffer with formaldehyde and then coprecipitated with alum (potassium aluminum sulfate) to form bulk vaccine adjuvanted with amorphous aluminum hydroxyphosphate sulfate. Each dose contains less than 1% yeast protein. The vaccine produced by the Merck method has been shown to be comparable to the plasma-derived vaccine in terms of animal potency (mouse, monkey, and chimpanzee) and protective efficacy (chimpanzee and human).

The vaccine against hepatitis B, prepared from recombinant yeast cultures, is free of association with human blood or blood products.

RECOMBIVAX HB Hepatitis B Vaccine (Recombinant) is supplied in three formulations. [See How Supplied/Storage and Handling (16).]

Pediatric/Adolescent Formulation (Without Preservative), 10 mcg/mL: each 0.5 mL dose contains 5 mcg of hepatitis B surface antigen.

Adult Formulation (Without Preservative), 10 mcg/mL: each 1 mL dose contains 10 mcg of hepatitis B surface antigen.

Dialysis Formulation (Without Preservative), 40 mcg/mL: each 1 mL dose contains 40 mcg of hepatitis B surface antigen.

All formulations contain approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate, previously referred to as aluminum hydroxide) per mL of vaccine. In each formulation, hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate) per mL of vaccine. The vaccine contains <15 mcg/mL residual formaldehyde. The vaccine is of the *adw* subtype.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

RECOMBIVAX HB has been shown to elicit antibodies to hepatitis B virus as measured by ELISA. Antibody concentrations ≥10mIU/mL against HBsAg are recognized as conferring protection against hepatitis B infection.{2}

Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

RECOMBIVAX HB has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility [see Use in Specific Populations (8)].

14 CLINICAL STUDIES

14.1 Efficacy in Neonates with Peripartum Exposure to Hepatitis B

The protective efficacy of three 5 mcg doses of RECOMBIVAX HB has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg (a core-associated antigenic complex which correlates with high infectivity). In a clinical study of infants who received one dose of HBIG at birth followed by the recommended three-dose regimen of RECOMBIVAX HB, chronic infection had not occurred in 96% of 130 infants after nine months of follow-up.{4} The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in untreated historical controls.{5} Significantly fewer neonates became chronically infected when given one dose of HBIG at birth followed by the recommended three-dose regimen of RECOMBIVAX HB when compared to historical controls who received only a single dose of HBIG.{6} As demonstrated in the above study, HBIG, when administered simultaneously with RECOMBIVAX HB at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the vaccine.{6}

14.2 Immunogenicity of a Three-Dose Regimen in Healthy Infants, Children, and Adolescents

Three 5 mcg doses of RECOMBIVAX HB induced a protective level of antibody in 100% of 92 infants, 99% of 129 children, and in 99% of 112 adolescents [see Dosage and Administration (2.3)].

14.3 Immunogenicity of a Two-Dose Regimen in Healthy Adolescents 11 through 15 Years of Age

For adolescents (11 through 15 years of age), the immunogenicity of a two-dose regimen (10 mcg at 0 and 4-6 months) was compared with that of the standard three-dose regimen (5 mcg at 0, 1, and 6 months) in an open, randomized, multicenter study. The proportion of adolescents receiving the two-dose regimen who developed a protective level of antibody one month after the last dose (99% of 255 subjects) appears similar to that among adolescents who received the three-dose regimen (98% of 121 subjects). After adolescents (11 through 15 years of age) received the first 10-mcg dose of the two-dose regimen, the proportion who developed a protective level of antibody was approximately 72%.

14.4 Immunogenicity in Healthy Adults

Clinical studies have shown that RECOMBIVAX HB when injected into the deltoid muscle induced protective levels of antibody in 96% of 1213 healthy adults who received the recommended three-dose regimen. Antibody responses varied with age; a protective level of antibody was induced in 98% of 787 young adults 20-29 years of age, 94% of 249 adults 30-39 years of age and in 89% of 177 adults ≥40 years of age.

14.5 Efficacy and Immunogenicity in Specific Populations

Chronic Hepatitis C Infection

In one published study, the seroprotection rates in individuals with chronic hepatitis C virus (HCV) infection given the standard regimen of RECOMBIVAX HB was approximately 70%.{7} In a second published study of intravenous drug users given an accelerated schedule of RECOMBIVAX HB, infection with HCV did not affect the response to RECOMBIVAX HB.{8}

Predialysis and Dialysis Adult Patients

Predialysis and dialysis adult patients respond less well to hepatitis B vaccines than do healthy individuals; however, vaccination of adult patients early in the course of their renal disease produces higher seroconversion rates than vaccination after dialysis has been initiated.{9} In addition, the responses to these vaccines may be lower if the vaccine is administered as a buttock injection. When 40 mcg of Hepatitis B Vaccine (Recombinant), was administered in the deltoid muscle, 89% of 28 participants developed anti-HBs with 86% achieving levels ≥10 mIU/mL. However, when the same dosage of this vaccine was administered inappropriately either in the buttock or a combination of buttock and deltoid, 62% of 47 participants developed anti-HBs with 55% achieving levels of ≥10 mIU/mL.

15 REFERENCES

 CDC. A Comprehensive Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part I: Immunization of Infants, Children and Adolescents. MMWR Recommendations and Reports 2005; 54(RR16): 1-23. Appendix C - Postexposure Prophylaxis of

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RECOMBIVAX HB (pediatric and adult) FORMULATION is available in single-dose vials and prefilled Luer-Lok® syringes.

RECOMBIVAX HB DIALYSIS FORMULATION is available in single-dose vials.

Pediatric/Adolescent Formulation (PRESERVATIVE FREE)

0.5 mL (5 mcg) in single-dose vials and prefilled Luer-Lok® syringes

NDC 0006-4981-00 - box of ten 0.5-mL single-dose vials

Color coded with a yellow cap and stripe on the vial labels and cartons and an orange banner on the vial labels and cartons

NDC 0006-4093-02 - carton of 10 prefilled single-dose Luer-Lok® syringes with tip caps

Color coded with a yellow plunger rod

Adult Formulation (PRESERVATIVE FREE)

1 mL (10mcg) in single-dose vials and prefilled Luer-Lok® syringes

NDC 0006-4995-00 – 1-mL single dose vial

Color coded with a green cap and stripe

NDC 0006-4995-41 – box of ten 1-mL single-dose vials

Color coded with a green cap and stripe

NDC 0006-4094-02 – carton of 10 pre-filled single-dose syringes with tip caps

Color coded with a green plunger rod

RECOMBIVAX HB DIALYSIS FORMULATION

1 mL (40mcg) in single-dose vials

NDC 0006-4992-00 - 1-mL single-dose vial

Color coded with a blue cap and stripe

16.2 Storage and Handling

- Protect from light.
- Store vials and syringes at 2-8°C (36-46°F).
- Do not freeze since freezing destroys potency.
- RECOMBIVAX HB is stable at temperatures from 0° to 25° C (32° to 75°F) for 72 hours. These
 data are not recommendations for shipping or storage but may guide decisions for use in case of
 temporary temperature excursions.

17 PATIENT COUNSELING INFORMATION

Information for Vaccine Recipients and Parents/Guardians

- Inform the patient, parent or guardian of the potential benefits and risks associated with vaccination, as well as the importance of completing the immunization series.
- Question the vaccine recipient, parent or guardian about the occurrence of any symptoms and/or signs of adverse reaction after a previous dose of hepatitis B vaccine.
- Tell the patient, parent or guardian to report adverse events to the physician or clinic where the vaccine was administered.
- Prior to vaccination, give the patient, parent or guardian the Vaccine Information Statements which are required by the National Vaccine Injury Act of 1986. The materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Tell the patient, parent or guardian that the United States Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events by the National Childhood Vaccine Injury Act of 1986. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at (www.vaers.hhs.gov).

Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of **MERCK & CO., INC.,** Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

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uspi-v232-i-1812r440

EXHIBIT 243

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These highlights do not include all the information needed to use PREVNAR 13 safely and effectively. See full prescribing information for PREVNAR 13.

PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein])
Suspension for intramuscular injection
Initial US Approval: 2010

| RECENT MAJOR CHANGES | |
|---|--------|
| Indications and Usage (1.3) | 7/2016 |
| Vaccination Schedule for Children Previously | |
| Vaccinated With Prevnar Pneumococcal 7-valent | |
| Conjugate Vaccine (Diphtheria CRM ₁₉₇ Protein) (2.5) Removal | 3/2017 |
| Vaccination Schedule for Adults 18 Years of Age | |
| and Older (2.6) | 7/2016 |
| Contraindications (4) | 7/2016 |
| INDICATIONS AND USAGE | |

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 is indicated for:

- active immunization for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1.1)
- active immunization for the prevention of otitis media caused by S. pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A. (1.1)

In children 6 years through 17 years of age (prior to the 18th birthday), Prevnar 13 is indicated for:

active immunization for the prevention of invasive disease caused by S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1.2)

In adults 18 years of age and older, Prevnar 13 is indicated for:

 active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1.3)

Limitations of Prevnar 13 Use and Effectiveness

• Prevnar 13 does not protect against disease caused by *S. pneumoniae* serotypes that are not in the vaccine. (1.4)

----- DOSAGE AND ADMINISTRATION -----

Children 6 weeks through 5 years: The four-dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6, and 12-15 months of age. (2.3)

Children 6 through 17 years of age: a single dose. (2.5) Adults 18 years and older: a single dose. (2.6)

-----DOSAGE FORMS AND STRENGTHS -----

0.5 mL suspension for intramuscular injection, supplied in a single-dose prefilled syringe. (3)

-----CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine. (4)

----- WARNINGS AND PRECAUTIONS-----

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.3)

----- -- -- -- -- -- -- -- ADVERSE REACTIONS-----

- In infants and toddlers vaccinated at 2, 4, 6, and 12-15 months of age in US clinical trials, the most commonly reported solicited adverse reactions (>5%) were irritability (>70%), injection site tenderness (>50%), decreased appetite (>40%), decreased sleep (>40%), increased sleep (>40%), fever (>20%), injection site redness (>20%), and injection site swelling (>20%). (6.1)
- In children aged 5 through 17 years, the most commonly reported solicited adverse reactions (>5%) were injection site tenderness (>80%), injection site redness (>30%), injection site swelling (>30%), irritability (>20%), decreased appetite (>20%), increased sleep (>20%), fever (>5%), and decreased sleep (>5%). (6.1)
- In adults aged 18 years and older, the most commonly reported solicited adverse reactions (>5%) were pain at the injection site (>50%), fatigue (>30%), headache (>20%), muscle pain (>20%), joint pain (>10%), decreased appetite (>10%), injection site redness (>10%), injection site swelling (>10%), limitation of arm movement (>10%), vomiting (>5%), fever (>5%), chills (>5%), and rash (>5%). (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-438-1985 or VAERS at 1-800-822-7967 or http://vaers.hhs.gov.

----- USE IN SPECIFIC POPULATIONS -----

Pediatric Use: Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Children 6 Weeks Through 5 Years of Age

In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13[®] is indicated for:

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae se*rotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A.

1.2 Children 6 Years Through 17 Years of Age

In children 6 years through 17 years of age (prior to the 18th birthday), Prevnar 13 is indicated for:

• active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

1.3 Adults 18 Years of Age and Older

In adults 18 years of age and older, Prevnar 13 is indicated for:

• active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

1.4 Limitations of Prevnar 13 Use and Effectiveness

• Prevnar 13 does not protect against disease caused by *S. pneumoniae* serotypes that are not in the vaccine.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Since this product is a suspension containing an adjuvant, shake vigorously immediately prior to use to obtain a homogenous, white suspension in the vaccine container. Do not use the vaccine if it cannot be resuspended. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration [see Description (11)]. This product should not be used if particulate matter or discoloration is found.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

2.2 Administration Information

For intramuscular injection only.

Each 0.5 mL dose is to be injected intramuscularly using a sterile needle attached to the supplied prefilled syringe. The preferred sites for injection are the anterolateral aspect of the thigh in infants and the deltoid muscle of the upper arm in toddlers, children and adults. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

2.3 Vaccination Schedule for Infants and Toddlers

Prevnar 13 is to be administered as a four-dose series at 2, 4, 6, and 12-15 months of age.

Table 1: Vaccination Schedule for Infants and Toddlers

| Dose | Dose 1 ^{a,b} | Dose 2 ^b | Dose 3 ^b | Dose 4 ^c |
|-------------|-----------------------|---------------------|---------------------|---------------------|
| Age at Dose | 2 months | 4 months | 6 months | 12-15 months |
| | | | | |
| | | | | |

^a Dose 1 may be given as early as 6 weeks of age.

2.4 Vaccination Schedule for Unvaccinated Children 7 Months Through 5 Years of Age

For children 7 months through 5 years of age who have not received Prevnar[®] or Prevnar 13, the catch-up schedule in Table 2 applies:

Table 2: Vaccination Schedule for Unvaccinated Children 7 Months of Age Through 5 Years of Age

| Age at First Dose | Total Number of 0.5 mL Doses |
|--|------------------------------|
| 7-11 months of age | 3ª |
| 12-23 months of age | 2 ^b |
| 24 months through 5 years of age (prior to the 6 th birthday) | 1 |

^a The first 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months.

The immune responses induced by this catch-up schedule may result in lower antibody concentrations for some serotypes, compared to antibody concentrations following 4 doses of Prevnar 13 (given at 2, 4, 6, and 12-15 months). In children 24 months through 5 years of age, lower antibody concentrations were observed for some serotypes, compared to antibody concentrations following 3 doses of Prevnar 13 (given at 2, 4, and 6 months).

2.5 Vaccination Schedule for Children 6 Years Through 17 Years of Age

In children 6 years through 17 years of age, Prevnar 13 is administered as single dose. If Prevnar was previously administered, then at least 8 weeks should elapse before receiving Prevnar 13.

^bThe recommended dosing interval is 4 to 8 weeks.

^c The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

^bTwo doses at least 2 months apart.

2.6 Vaccination Schedule for Adults 18 Years of Age and Older

Prevnar 13 is administered as a single dose.

3 DOSAGE FORMS AND STRENGTHS

Prevnar 13 is a suspension for intramuscular injection available in 0.5 mL single-dose prefilled syringes.

4 CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 13 or any diphtheria toxoid-containing vaccine [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of Prevnar 13.

5.2 Altered Immunocompetence

Individuals with altered immunocompetence, including those at higher risk for invasive pneumococcal disease (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, hematopoietic stem cell transplant, nephrotic syndrome), may have reduced antibody responses to immunization with Prevnar 13 [see Use in Specific Populations (8.6)].

5.3 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

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6.1 Clinical Trials Experience With Prevnar 13 in Children 6 Weeks Through 17 Years of Age

The safety of Prevnar 13 was evaluated in 13 clinical trials in which 4,729 infants (6 weeks through 11 months of age) and toddlers (12 months through 15 months of age) received at least one dose of Prevnar 13 and 2,760 infants and toddlers received at least one dose of Prevnar active control. Safety data for the first three doses are available for all 13 infant studies; dose 4 data are available for 10 studies; and data for the 6-month follow-up are available for 7 studies. The vaccination schedule and concomitant vaccinations used in these infant trials were consistent with country-specific recommendations and local clinical practice. There were no substantive differences in demographic characteristics between the vaccine groups. By race, 84.0% of subjects were White, 6.0% were Black or African-American, 5.8% were Asian and 3.8% were of 'Other' race (most of these being biracial). Overall, 52.3% of subjects were male infants.

Three studies in the US (Studies 1, 2 and 3)^{1,2,3} evaluated the safety of Prevnar 13 when administered concomitantly with routine US pediatric vaccinations at 2, 4, 6, and 12-15 months of age. Solicited local and systemic adverse reactions were recorded daily by parents/guardians using an electronic diary for 7 consecutive days following each vaccination. For unsolicited adverse events, study subjects were monitored from administration of the first dose until one month after the infant series, and for one month after the administration of the toddler dose. Information regarding unsolicited and serious adverse events, newly diagnosed chronic medical conditions, and hospitalizations since the last visit were collected during the clinic visit for the fourth-study dose and during a scripted telephone interview 6 months after the fourth-study dose. Serious adverse events were also collected throughout the study period. Overall, the safety data show a similar proportion of Prevnar 13 and Prevnar subjects reporting serious adverse events. Among US study subjects, a similar proportion of Prevnar 13 and Prevnar recipients reported solicited local and systemic adverse reactions as well as unsolicited adverse events.

Serious Adverse Events in All Infant and Toddler Clinical Studies

Serious adverse events were collected throughout the study period for all 13 clinical trials. This reporting period is longer than the 30-day post-vaccination period used in some vaccine trials. The longer reporting period may have resulted in serious adverse events being reported in a higher percentage of subjects than for other vaccines. Serious adverse events reported following vaccination in infants and toddlers occurred in 8.2% among Prevnar 13 recipients and 7.2% among Prevnar recipients. Serious adverse events observed during different study periods for Prevnar 13 and Prevnar respectively were: 1) 3.7% and 3.5% from dose 1 to the blood draw approximately 1 month after the infant series; 2) 3.6% and 2.7% from the blood draw after the infant series to the toddler dose; 3) 0.9% and 0.8% from the toddler dose to the blood draw approximately 1 month after the toddler dose and 4) 2.5% and 2.8% during the 6 month follow-up period after the last dose.

The most commonly reported serious adverse events were in the 'Infections and infestations' system organ class including bronchiolitis (0.9%, 1.1%), gastroenteritis, (0.9%, 0.9%), and pneumonia (0.9%, 0.5%) for Prevnar 13 and Prevnar respectively.

There were 3 (0.063%) deaths among Prevnar 13 recipients, and 1 (0.036%) death in Prevnar recipients, all as a result of sudden infant death syndrome (SIDS). These SIDS rates are consistent with published age specific background rates of SIDS from the year 2000.

Among 6,839 subjects who received at least 1 dose of Prevnar 13 in clinical trials conducted globally, there was 1 hypotonic-hyporesponsive episode adverse reaction reported (0.015%). Among 4,204 subjects who received at least 1 dose of Prevnar in clinical trials conducted globally, there were 3 hypotonic-hyporesponsive episode adverse reactions reported (0.071%). All 4 events occurred in a single clinical trial in Brazil in which subjects received whole cell pertussis vaccine at the same time as Prevnar 13 or Prevnar.

Solicited Adverse Reactions in the Three US Infant and Toddler Studies

A total of 1,907 subjects received at least 1 dose of Prevnar 13 and 701 subjects received at least 1 dose of Prevnar in the three US studies (Studies 1, 2 and 3)^{1,2,3}. Most subjects were White (77.3%), 14.2% were Black or African-American, and 1.7% were Asian; 79.1% of subjects were non-Hispanic and non-Latino and 14.6% were Hispanic or Latino. Overall, 53.6% of subjects were male infants.

The incidence and severity of solicited adverse reactions that occurred within 7 days following each dose of Prevnar 13 or Prevnar administered to US infants and toddlers are shown in Tables 3 and 4.

Table 3: Percentage of US Infant and Toddler Subjects Reporting Solicited Local Reactions at the Prevnar 13 or Prevnar Injection Sites Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age^a

| Within / Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age | | | | | | | | | |
|--|--|---|--|---|---|---|---|---|--|
| | Dose 1 | | Dose 2 | | Do | Dose 3 | | Dose 4 | |
| Graded Local Reaction | Prevnar 13 (N ^b =1375- 1612) % | Prevnar (N ^b =516- 606) % | Prevnar 13 (N ^b =1069- 1331) % | Prevnar (N ^b =405- 510) % | Prevnar 13 (N ^b =998- 1206) % | Prevnar (N ^b =348- 446) % | Prevnar 13 (N ^b =874- 1060) % | Prevnar (N ^b =283- 379) % | |
| Redness ^c | | | | | | | | | |
| Any | 24.3 | 26.0 | 33.3 | 29.7 | 37.1 | 36.6 | 42.3 | 45.5 | |
| Mild | 23.1 | 25.2 | 31.9 | 28.7 | 35.3 | 35.3 | 39.5 | 42.7 | |
| Moderate | 2.2 | 1.5 | 2.7 | 2.2 | 4.6 | 5.1 | 9.6 | 13.4 ^d | |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| Swelling ^c | | | | | | | | | |
| Any | 20.1 | 20.7 | 25.2 | 22.5 | 26.8 | 28.4 | 31.6 | 36.0 ^d | |
| Mild | 17.2 | 18.7 | 23.8 | 20.5 | 25.2 | 27.5 | 29.4 | 33.8 | |
| Moderate | 4.9 | 3.9 | 3.7 | 4.9 | 3.8 | 5.8 | 8.3 | 11.2 ^d | |
| Severe | 0 | 0 | 0.1 | 0 | 0 | 0 | 0 | 0 | |
| Tenderness | | | | | | | | | |
| Any | 62.5 | 64.5 | 64.7 | 62.9 | 59.2 | 60.8 | 57.8 | 62.5 | |
| Interferes with limb movement | 10.4 | 9.6 | 9.0 | 10.5 | 8.4 | 9.0 | 6.9 | 5.7 | |

^a Data are from three primary US safety studies (the US Phase 2 infant study [National Clinical Trial (NCT) number NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

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^b Number of subjects reporting Yes for at least 1 day or No for all days.

^c Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of induration and erythema were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

^d Statistically significant difference p <0.05. No adjustments for multiplicity.

Table 4: Percentage of US Infant and Toddler Subjects Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination at 2, 4, 6, and 12-15 Months of Age^{a,b}

| vaccination at 2, 4, 0, and 12-15 World's of Age | | | | | | | | |
|--|---|---|--|---|---|---|---|---|
| | Dose | :1 | Dose | 2 | Dose 3 | | Dose | 4 |
| Graded Systemic Events | Prevnar 13 (N ^a =1360 - 1707) % | Prevnar (N ^a =497- 640) % | Prevnar 13 (N ^a =1084- 1469) % | Prevnar (N ^a =409- 555) % | Prevnar 13 (N ^a =997- 1361) % | Prevnar (N ^a =354- 521) % | Prevnar 13 (N ^a =850- 1227) % | Prevnar (N ^a =278- 436) % |
| Fever ^c | | | | | | | | |
| Any | 24.3 | 22.1 | 36.5 | 32.8 | 30.3 | 31.6 | 31.9 | 30.6 |
| Mild | 23.6 | 21.7 | 34.9 | 31.6 | 29.1 | 30.2 | 30.3 | 30.0 |
| Moderate | 1.1 | 0.6 | 3.4 | 2.8 | 4.2 | 3.3 | 4.4 | 4.6 |
| Severe | 0.1 | 0.2 | 0.1 | 0.3 | 0.1 | 0.7 | 1.0 | 0 |
| Decreased appetite | 48.3 | 43.6 | 47.8 | 43.6 | 47.6 | 47.6 | 51.0 | 49.4 |
| Irritability | 85.6 | 83.6 | 84.8 | 80.4 | 79.8 | 80.8 | 80.4 | 77.8 |
| Increased sleep | 71.5 | 71.5 | 66.6 | 63.4 | 57.7 | 55.2 | 48.7 | 55.1 |
| Decreased sleep | 42.5 | 40.6 | 45.6 | 43.7 | 46.5 | 47.7 | 45.3 | 40.3 |

^a Number of subjects reporting Yes for at least 1 day or No for all days.

The incidence rates of any fever ($\geq 38.0^{\circ}$ C) were similar on days 1 and 2 following each dose of Prevnar 13 compared to after each dose of Prevnar administered to US infants and toddlers (day 1 = day of vaccination). After dose 1, fever was reported in 11.0-12.7% on day 1 and 6.4-6.8% on day 2. After dose 2, fever was reported in 12.3-13.1% on day 1 and 12.5-12.8% on day 2. After dose 3, fever was reported in 8.0-9.6% on day 1 and 9.1-10.5% on day 2. And after dose 4, fever was reported in 6.3-6.4% on day 1 and 7.3-9.7% on day 2.

Unsolicited Adverse Reactions in the Three US Infant and Toddler Safety Studies

The following were determined to be adverse drug reactions based on experience with Prevnar 13 in clinical trials.

Reactions occurring in greater than 1% of infants and toddlers: diarrhea, vomiting, and rash.

Reactions occurring in less than 1% of infants and toddlers: crying, hypersensitivity reaction (including face edema, dyspnea, and bronchospasm), seizures (including febrile seizures), and urticaria or urticaria-like rash.

^b Data are from three primary US safety studies (the US Phase 2 infant study [NCT00205803] Study 1, the US noninferiority study [NCT00373958] Study 2, and the US lot consistency study [NCT00444457] Study 3). All infants received concomitant routine infant immunizations. Concomitant vaccines and pneumococcal conjugate vaccines were administered in different limbs.

^c Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (>40°C). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 62 to 75% of subjects after any of the 4 doses. There were no statistical differences in frequencies of adverse reactions reported between the Prevnar 13 and Prevnar groups.

Safety Assessments in the Catch-Up Studies in Infants and Children Through 5 Years of Age

In a catch-up study⁴ conducted in Poland (Study 4), 354 children (7 months through 5 years of age) receiving at least one dose of Prevnar 13 were also monitored for safety. All subjects in this study were White and non-Hispanic. Overall, 49.6% of subjects were male infants. The incidence and severity of solicited adverse reactions that occurred within 4 days following each dose of Prevnar 13 administered to pneumococcal-vaccine naïve children 7 months through 5 years of age are shown in Tables 5 and 6.

Table 5: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Local Reactions Within 4 Days After
Each Catch-Up Prevnar 13 Vaccination^a

| | 7 | through 11 mo | nths | 12 through 23 months | | 24 months through 5 years | |
|-------------------------------|------------------------------|--|--|--|---|---|--|
| Graded Local Reaction | Dose 1 N ^b =86 | Dose 2 N ^b =86-87 | Dose 3 N ^b =78-82 | Dose 1 N ^b =108-110 | Dose 2 N ^b =98-106 | Dose 1 N ^b =147-149 % | |
| Redness ^c | | | | | | | |
| Any | 48.8 | 46.0 | 37.8 | 70.0 | 54.7 | 50.0 | |
| Mild | 41.9 | 40.2 | 31.3 | 55.5 | 44.7 | 37.4 | |
| Moderate | 16.3 | 9.3 | 12.5 | 38.2 | 25.5 | 25.7 | |
| Severe | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| Swelling ^c | | I. | I. | 1 | | | |
| Any | 36.0 | 32.2 | 25.0 | 44.5 | 41.0 | 36.9 | |
| Mild | 32.6 | 28.7 | 20.5 | 36.7 | 36.2 | 28.2 | |
| Moderate | 11.6 | 14.0 | 11.3 | 24.8 | 12.1 | 20.3 | |
| Severe | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| Tenderness | • | L | L | • | 1 | | |
| Any | 15.1 | 15.1 | 15.2 | 33.3 | 43.7 | 42.3 | |
| Interferes with limb movement | 1.2 | 3.5 | 6.4 | 0.0 | 4.1 | 4.1 | |

^a Study conducted in Poland (NCT00452452) Study 4.

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^b Number of subjects reporting Yes for at least 1 day or No for all days.

^c Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

Table 6: Percentage of Subjects 7 Months Through 5 Years of Age Reporting Solicited Systemic
Adverse Reactions Within 4 Days After Each Catch-Up Prevnar 13 Vaccination^a

| | 7 | through 11 mont | hs | 12 through 23 months | | 24 months through 5 years |
|--------------------|--|--|--|--------------------------------------|--|---|
| Systemic Reaction | Dose 1 N ^b =86-87 | Dose 2 N ^b =86-87 | Dose 3 N ^b =78-81 | Dose 1 N ^b =108 | Dose 2 N ^b =98-100 % | Dose 1 N ^b =147-148 % |
| Fever ^c | 1 | I | I | | 1 | |
| Mild | 3.4 | 8.1 | 5.1 | 3.7 | 5.1 | 0.7 |
| Moderate | 1.2 | 2.3 | 1.3 | 0.9 | 0.0 | 0.7 |
| Severe | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Decreased appetite | 19.5 | 17.2 | 17.5 | 22.2 | 25.5 | 16.3 |
| Irritability | 24.1 | 34.5 | 24.7 | 30.6 | 34.0 | 14.3 |
| Increased sleep | 9.2 | 9.3 | 2.6 | 13.0 | 10.1 | 11.6 |
| Decreased sleep | 24.1 | 18.4 | 15.0 | 19.4 | 20.4 | 6.8 |

^a Study conducted in Poland (NCT00452452) Study 4.

A US study⁵ (Study 5) evaluated the use of Prevnar 13 in children previously immunized with Prevnar. In this open label trial, 596 healthy children 15 through 59 months of age previously vaccinated with at least 3 doses of Prevnar, received 1 or 2 doses of Prevnar 13. Children 15 months through 23 months of age (group 1) received 2 doses, and children 24 months through 59 months of age (group 2) received one dose. Most subjects were White (74.3%), 14.9% were Black or African-American, and 1.2% were Asian; 89.3% of subjects were non-Hispanic and non-Latino and 10.7% were Hispanic or Latino. Overall, 52.2% of subjects were male.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 15 months through 59 months of age are shown in Tables 7 and 8.

^b Number of subjects reporting Yes for at least 1 day or No for all days.

^c Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (>40°C). No other systemic event other than fever was graded.

Table 7: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4
Prior Infant Doses of Prevnar, Reporting Solicited Local Reactions Within 7 Days After One
Supplemental Prevnar 13 Vaccination^a

| | 15 months the | 24 months through 59 months | |
|-------------------------------|--|--|---|
| Graded Local Reaction | 1 dose Prevnar 13 3 prior Prevnar doses N ^d =67-72 % | 1 dose Prevnar 13 4 prior Prevnar doses N ^d =154-184 % | 1 dose Prevnar 13 3 or 4 prior Prevnar doses N ^d =209-238 % |
| Redness ^e | | ' | |
| Any | 26.4 | 28.2 | 35.4 |
| Mild | 18.8 | 24.3 | 31.1 |
| Moderate | 11.4 | 7.5 | 12.1 |
| Severe | 1.5 | 0.0 | 0.0 |
| Swelling ^e | ' | ' | 1 |
| Any | 23.9 | 19.6 | 20.7 |
| Mild | 18.6 | 16.4 | 17.2 |
| Moderate | 8.8 | 8.1 | 7.5 |
| Severe | 0.0 | 0.0 | 0.0 |
| Tenderness | • | • | - |
| Any | 48.6 | 47.3 | 62.6 |
| Interferes with limb movement | 5.9 | 6.4 | 10.7 |

^a Study conducted in US NCT00761631 (Study 5).

Table 8: Percentage of Subjects 15 Months Through 59 Months of Age, Previously Vaccinated With 3 or 4
Prior Infant Prevnar Doses, Reporting Solicited Systemic Adverse Reactions Within 7 Days After One
Supplemental Prevnar 13 Vaccination^a

| | 15 through | 24 months through 59 months ^c | |
|----------------------|--|--|---|
| Systemic Reaction | 1 dose Prevnar 13 3 prior Prevnar doses N ^d =66-75 % | 1 dose Prevnar 13 4 prior Prevnar doses N ^d =154-189 % | 1 dose Prevnar 13 3 or 4 prior Prevnar doses N ^d =209-236 % |
| Fever ^e | | | |
| Any | 19.1 | 19.9 | 8.1 |
| Mild | 16.2 | 17.4 | 7.6 |
| Moderate | 6.1 | 3.9 | 1.9 |
| Severe | 0.0 | 0.0 | 0.5 |
| Decreased appetite | 44.4 | 39.3 | 28.1 |
| Irritability | 73.3 | 65.1 | 45.8 |
| Increased sleep | 35.2 | 35.3 | 18.8 |
| Decreased sleep | 25.0 | 29.7 | 14.8 |

^a Study conducted in US NCT00761631 (Study 5).

^b Dose 2 data not shown.

^c The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.

^d Number of subjects reporting Yes for at least 1 day or No for all days.

^e Diameters were measured in caliper units of whole numbers from 1 to 14 or 14+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild (0.5-2.0 cm), Moderate (2.5-7.0 cm), or Severe (>7.0 cm).

^b Dose 2 data not shown.

^c The data for this age group are only represented as a single result as 95% of children received 4 doses of Prevnar prior to enrollment.

^d Number of subjects reporting Yes for at least 1 day or No for all days.

^e Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (>40°C). No other systemic event other than fever was graded.

Clinical Trials Experience With Prevnar 13 in Children 5 Through 17 Years of Age

In a US study⁵ (Study 5), the safety of Prevnar 13 was evaluated in children 5 through 9 years of age previously immunized with at least one dose of Prevnar, and in children 10 through 17 years of age with no prior pneumococcal vaccination. In this open label trial, 592 children, including those with asthma, received a single dose of Prevnar 13. The percentage of children 5 through 9 years of age who received 3 and 4 prior doses of Prevnar was 29.1% and 54.5% respectively.

Most subjects were White (72.8%), 21.8% were Black or African-American, and 1.5% were Asian; 91.4% of subjects were non-Hispanic and non-Latino and 8.6% were Hispanic or Latino. Overall, 51.2% of subjects were male.

The incidence and severity of solicited adverse reactions that occurred within 7 days following one dose of Prevnar 13 administered to children 5 through 17 years of age are shown in Tables 9 and 10.

Table 9: Percentage of Subjects 5 Through 17 Years of Age, Reporting Solicited Local Reactions Within 7 Days After Prevnar 13 Vaccination ^a

| | Vaccine Group (as Administered) | | | | | | |
|--------------------------|---------------------------------|------------------------------|------|----------------|-----------------------------|-------|--|
| | (| Prevnar 13 5 Through 9 Ye | | (10 | Prevnar 13 Through 17 Ye | ears) | |
| Local Reaction | N ^b | n° | % | N ^b | n° | % | |
| Redness | | | | | | | |
| Any | 233 | 100 | 42.9 | 232 | 70 | 30.2 | |
| Mild ^d | 226 | 63 | 27.9 | 226 | 48 | 21.2 | |
| Moderate ^d | 218 | 48 | 22.0 | 221 | 31 | 14.0 | |
| Severe ^d | 212 | 7 | 3.3 | 213 | 4 | 1.9 | |
| welling | | | | | | | |
| Any | 226 | 85 | 37.6 | 233 | 86 | 36.9 | |
| Mild ^d | 220 | 48 | 21.8 | 221 | 50 | 22.6 | |
| Moderate ^d | 219 | 48 | 21.9 | 226 | 48 | 21.2 | |
| Severe ^d | 211 | 7 | 3.3 | 214 | 4 | 1.9 | |
| Cenderness | | | | | | | |
| Any | 265 | 230 | 86.8 | 283 | 252 | 89.0 | |
| Significant ^e | 221 | 43 | 19.5 | 242 | 106 | 43.8 | |

^a Study conducted in US NCT00761631 (Study 5).

N = number of subjects reporting Yes for at least 1 day or No for all days.

 $^{^{}c}$ n = Number of subjects reporting the specific characteristic.

^d Mild, 0.5 - 2.0 cm; moderate, 2.5 - 7.0 cm; severe, >7.0 cm.

Significant = present and interfered with limb movement.

Table 10: Percentage of Subjects 5 Through 17 Years of Age, Reporting Solicited Systemic Adverse Reactions Within 7 Days After
Prevnar 13 Vaccination^a

| | | Vaccine Group (as Administered) | | | | | | |
|-----------------------|-----------------------------------|---------------------------------|------|-------------------------------------|----|------|--|--|
| | Prevnar 13 (5 Through 9 Years) | | | Prevnar 13 (10 Through 17 Years) | | ars) | | |
| Systemic Event | N ^b | n° | % | N^{b} | n° | % | | |
| Any fever ≥38°C | 214 | 13 | 6.1 | 214 | 12 | 5.6 | | |
| Mild ^d | 212 | 9 | 4.2 | 214 | 11 | 5.1 | | |
| Moderate ^d | 212 | 5 | 2.4 | 212 | 1 | 0.5 | | |
| Severe ^d | 210 | 1 | 0.5 | 212 | 1 | 0.5 | | |
| Decreased appetite | 227 | 52 | 22.9 | 223 | 51 | 22.9 | | |
| Irritability | 234 | 73 | 31.2 | 234 | 59 | 25.2 | | |
| Increased sleep | 226 | 48 | 21.2 | 229 | 61 | 26.6 | | |
| Decreased sleep | 212 | 12 | 5.7 | 224 | 42 | 18.8 | | |
| Hives (urticaria) | 213 | 4 | 1.9 | 214 | 3 | 1.4 | | |

^a Study conducted in US NCT00761631 (Study 5).

6.2 Clinical Trials Experience With Prevnar 13 in Adults ≥18 Years of Age

The safety of Prevnar 13 was assessed in 7 clinical studies (Studies 6-12) ⁶⁻¹² conducted in the US and Europe which included 91,593 adults (48,806 received Prevnar 13) ranging in age from 18 through 101 years.

The 48,806 Prevnar 13 recipients included 899 adults who were aged 18 through 49 years, 2,616 adults who were aged 50 through 64 years, 45,291 adults aged 65 years and older. Of the 48,806 Prevnar 13 recipients, 46,890 adults had not previously received Pneumovax® 23 (pneumococcal polysaccharide vaccine [23-valent], PPSV23) ("PPSV23 unvaccinated") and 1,916 adults were previously vaccinated ("PPSV23 previously vaccinated") with PPSV23 at least 3 years prior to enrollment.

Safety and Immunogenicity Studies

Safety and immunogenicity of Prevnar 13 is supported by 6 clinical studies. Study 6⁶ evaluated the safety and immunogenicity of Prevnar 13 in adults 18 through 64 years of age who had not received a previous dose of pneumococcal vaccine. Adults 18 through 59 years of age received a single dose of Prevnar 13, and adults 60 through 64 years of age received a single dose of Prevnar 13 or PPSV23.

Study 7 was randomized and compared the safety and immunogenicity of Prevnar 13 with PPSV23 as a single dose in adults ≥70 years vaccinated with PPSV23 (≥5 years prior to enrollment). Study 8 was randomized and evaluated the safety and immunogenicity of Prevnar 13 and PPSV23 in different sequential order in PPSV23 naive adults aged 60 through 64 years 8.

One clinical safety study⁹ (Study 9) of Prevnar 13, conducted in PPSV23 previously vaccinated (\geq 3 years prior to enrollment) adults aged \geq 68 years was a single arm study. Two studies, one in the US¹⁰ (Study 10) in adults aged 50 through 59 years and the other in Europe¹¹ (Study 11) in adults aged \geq 65 years, evaluated the concomitant administration of Prevnar 13 with inactivated

^b N = number of subjects reporting Yes for at least 1 day or No for all days.

on = Number of subjects reporting the event.

^d Fever gradings: Mild (≥38°C but ≤39°C), Moderate (>39°C but ≤40°C), and Severe (>40°C). No other systemic event other than fever was graded. Parents reported the use of antipyretic medication to treat or prevent symptoms in 45.1% and 33.1% of subjects 5 through 9 years of age and 10 through 17 years of age, respectively.

influenza vaccine, trivalent (Fluarix $^{\text{®}}$, A/H1N1, A/H3N2, and B, Fall 2007/Spring 2008: IIV3) in these two age groups in PPSV23 unvaccinated adults.

The total safety population in the 6 safety and immunogenicity studies was 7,097. In 5 of the 6 safety and immunogenicity studies, more females than males were enrolled (50.2% - 61.8%). Across the 6 studies the racial distribution included: >85% White; 0.2%-10.7% Black or African American; 0%-1.7% Asian; <1% Native Hawaiian or other Pacific Islander; \leq 1%, American Indian or Alaskan Native. Ethnicity data were not collected in Study 11; in the 5 other studies 0.6%-4.8% were Hispanic or Latino.

In five studies, ^{6-8,10,11} subjects with pre-existing underlying diseases were enrolled if the medical condition was stable (did not require a change in therapy or hospitalization for worsening disease for 12 weeks before receipt of study vaccine) except in Study 9 where subjects were enrolled if the medical condition was stable for 6 or more weeks before receipt of study vaccine.

In the 6 safety and immunogenicity studies, ⁶⁻¹¹ subjects were excluded from study participation due to prior receipt of diphtheria toxoid-containing vaccines within 6 months of study vaccine. However, the time of prior receipt of a diphtheria toxoid-containing vaccine was not recorded.

Solicited adverse reactions for Prevnar 13 in the safety and immunogenicity studies were monitored by subjects recording local adverse reactions and systemic reactions daily using an electronic diary for 14 consecutive days following vaccination. Unsolicited serious and non-serious adverse events were collected for one month after each vaccination. In addition, serious adverse events were collected for an additional 5 months after each vaccination (at the 6-month follow-up phone contact) in all studies except Study 11.

Following licensure of Prevnar 13 in adults ≥50 years of age, a randomized, double-blind, placebo-controlled US study (Study 13) was conducted to evaluate concomitant administration of Prevnar 13 with inactivated influenza vaccine, quadrivalent (Fluzone[®] Quadrivalent, A/H1N1, A/H3N2, B/Brisbane, and B/Massachusetts, Fall 2014/Spring 2015: IIV4) in PPSV23 previously vaccinated adults ≥50 years of age. Unsolicited serious and non-serious adverse events were collected as described above for Studies 6-10.

Efficacy Study

Study 12^{12} was a randomized double-blind placebo-controlled study conducted in the Netherlands in community-dwelling adults aged 65 years and older with no prior pneumococcal vaccination history. A total of 84,496 subjects received either a single dose of Prevnar 13 (42,240) or placebo (42,256) in a 1:1 randomization. Among the 84,496 subjects, 58,072 (68.7%) were \geq 65 to <75 years of age, 23,481 (27.8%) were \geq 75 and <85 years of age, and 2,943 (3.5%) were \geq 85 years of age. In the total safety population, more males (55.9%) were enrolled than females. The racial distribution was 98.5% White, 0.3% Black, 0.7% Asian, 0.5% Other, with <0.1% having missing data.

Adults with immunocompromising conditions or receiving immunosuppressive therapy and adults residing in a long-term care facility or requiring semiskilled nursing care were excluded.

Adults with pre-existing medical conditions, as well as subjects with a history of smoking were eligible for enrollment. In the safety population, 42.3% of subjects had pre-existing medical conditions including heart disease (25.4%), lung disease or asthma (15.1%) and type 1 and type 2 diabetes mellitus (12.5%). Smoking was reported at baseline by 12.3% of the subjects.

For a subset of 2,011 subjects (1,006 Prevnar 13 recipients and 1,005 placebo recipients), solicited adverse reactions were monitored by recording local and systemic events using electronic diaries for 7 days after vaccination; unsolicited adverse events were collected for 28 days after vaccination, and serious adverse events were collected for 6 months after vaccination. For the remaining 41,231 Prevnar 13 and 41,250 placebo vaccinated subjects, serious adverse events were collected for 28 days after vaccination.

Serious Adverse Events in Adult Clinical Studies

Safety and Immunogenicity Studies

Across the 6 safety and immunogenicity studies, ⁶⁻¹¹ serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5,057 subjects vaccinated with Prevnar 13, and in 0.4%-1.7% of 1,124 subjects vaccinated after an initial study dose of PPSV23. From 1 month to 6 months after an initial study dose, serious adverse events were reported in 0.2%-5.8% of subjects vaccinated during the studies with Prevnar 13 and in 2.4%-5.5% of subjects vaccinated with PPSV23. One case of erythema multiforme occurred 34 days after receipt of a second dose of Prevnar 13.

Twelve of 5,667 (0.21%) Prevnar 13 recipients and 4 of 1,391 (0.29 %) PPSV23 recipients died. Deaths occurred between Day 3 and Day 309 after study vaccination with Prevnar 13 or PPSV23. Two of 12 deaths occurred within 30 days of vaccination and both deaths were in subjects >65 years of age. One death due to cardiac failure occurred 3 days after receiving placebo. This subject had received Prevnar 13 and IIV3 one month earlier. The other death was due to peritonitis 20 days after receiving Prevnar 13. The reported causes of the 10 remaining deaths occurring greater than 30 days after receiving Prevnar 13 were cardiac disorders (4), neoplasms (4), *Mycobacterium avium* complex pulmonary infection (1) and septic shock (1).

Efficacy Study

In Study 12¹² (subjects 65 years and older), serious adverse events within 1 month of vaccination were reported in 327 of 42,237 (0.8%) Prevnar 13 recipients (352 events) and in 314 of 42,225 (0.7%) placebo recipients (337 events). In the subset of subjects where serious adverse events were monitored for 6 months, 70 of 1,006 (7%) Prevnar 13 vaccinated subjects (90 events) and 60 of 1,005 (6%) placebo vaccinated subjects (69 events) reported serious adverse events.

During the follow-up period (average of 4 years) for case accumulation there were 3,006 deaths (7.1%) in the Prevnar 13 group and 3,005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Prevnar 13 group and 10 deaths (<0.1%) in the placebo group within 28 days of vaccination. There were 161 deaths (0.4%) in the Prevnar 13 group and 144 deaths

(0.3%) in the placebo group within 29 days – 6 months following vaccination. These data do not provide evidence for a causal relationship between deaths and vaccination with Prevnar 13.

Solicited Adverse Reactions in Adult Clinical Studies

The incidence and severity of solicited adverse reactions that occurred within 7 or 14 days following each dose of Prevnar 13, PPSV23, or placebo administered to adults in 5 studies are shown in Tables 11, 12, 13, and 14.

The commonly reported local adverse reactions after Prevnar 13 vaccination in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were redness, swelling and pain at the injection site, or limitation of arm movement (Tables 11 and 12). The commonly reported systemic adverse reactions in PPSV23 unvaccinated and PPSV23 previously vaccinated adults were fatigue, headache, chills, rash, decreased appetite, or muscle pain and joint pain (Tables 13 and 14).

Table 11 - Percentage of Subjects With Solicited Local Adverse Reactions Within 7 or 14 Days in PPSV23 Unvaccinated Adults^a

| | | Stu | dy 6 | | Stud | dy 8 | Study 12 | | |
|---|---------------------------------------|---|---------------------------------|-----------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------|--|
| Age in Years | 18-49 | 50-59 | 50-59 60-64 | | 60- | 60-64 | | 65 | |
| Local Reaction | Prevnar 13 ^b N°=266-787 | Prevnar 13 ^b N°=152-322 | Prevnar 13 N°=193-331 | PPSV23 N°=190-301 | Prevnar 13 N°=270-370 | PPSV23 N°=134-175 | Prevnar 13 N°=886-914 | Placebo N°=859-865 | |
| | % | % | % | % | % | % | % | % | |
| Redness ^d | | | | | | | | | |
| Any | 30.5 | 15.8 | 20.2 | 14.2 | 12.2 | 11.2 | 4.9 ^g | 1.2 | |
| Mild | 26.4 | 15.2 | 15.9 | 11.2 | 8.3 | 9.7 | 3.7 ^g | 0.8 | |
| Moderate | 11.9 | 5.0 | 8.6 | 4.9 | 6.4 | 3.9 | 1.7 ^g | 0.3 | |
| Severe | 2.8 | 0.7 | 1.7 | 0.0 | 1.2 | 0.8 | 0.5 | 0.1 | |
| Swelling ^d | | | | | | | | | |
| Any | 39.4 | 21.7 | 19.3 | 13.1 | 10.0 | 10.4 | 6.8 ^g | 1.2 | |
| Mild | 37.2 | 20.6 | 15.6 | 10.1 | 8.2 | 6.1 | 5.5 ^g | 0.7 | |
| Moderate | 15.1 | 4.3 | 8.2 | 4.4 | 3.8 | 7.6 | 2.6 ^g | 0.6 | |
| Severe | 1.4 | 0.0 | 0.6 | 1.1 | 0.0 | 0.0 | 0.1 | 0.1 | |
| Paine | | | | | | | | | |
| Any | 96.7 | 88.8 | 80.1 | 73.4 | 69.2 ^g | 58.3 | 36.1 ^g | 6.1 | |
| Mild | 93.2 | 85.9 | 78.6 ^g | 68.6 | 66.1 ^g | 52.9 | 32.9 ^g | 5.6 | |
| Moderate | 77.1 | 39.5 | 23.3 | 30.0 | 20.1 | 21.7 | 7.7 ^g | 0.6 | |
| Severe | 16.0 | 3.6 | 1.7 | 8.6 ^g | 2.3 | 0.8 | 0.3 | 0.1 | |
| Limitation of arm movement ^f | | | | | | | | | |
| Any | 75.2 | 40.7 | 28.5 | 30.8 | 23.5 | 28.2 | 14.1 ^g | 3.2 | |
| Mild | 71.5 | 38.6 | 26.9 | 29.3 | 22.7 | 26.1 | 12.4 ^g | 2.5 | |
| Moderate | 18.5 | 2.9 | 2.2 | 3.8 | 1.2 | 3.1 | 1.7 ^g | 0.5 | |
| Severe | 15.6 | 2.9 | 1.7 | 4.3 | 1.1 | 2.3 | 1.2 | 0.7 | |

^a Studies conducted in US NCT00427895 (Study 6) and NCT00574548 (Study 8) reported local reactions within 14 days. Study conducted in the Netherlands NCT00744263 (Study 12) reported local reactions within 7 days.

^b Open label administration of Prevnar 13.

^c Number of subjects with known values (number of subjects reporting yes for at least one day or no for all days).

 $^{^{}m d}$ Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and Severe is >10.0 cm.

^e Mild = awareness of symptom but easily tolerated, Moderate = discomfort enough to cause interference with usual activity, Severe = incapacitating with inability to do usual activity.

f Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder, and Severe = unable to move arm above shoulder.

^g Statistically significant difference p <0.05. No adjustments for multiplicity.

Table 12 - Percentage of Subjects With Solicited Local Adverse Reactions in PPSV23 Previously Vaccinated Adults^a

| | Stu | ıdy 7 | Study 9 |
|---|-------------------------------|---------------------------|--|
| Age in Years | 2 | 270 | ≥68 |
| Local Reaction | Prevnar 13 N°=306-362 % | PPSV23 N°=324-383 % | Prevnar 13 ^b N°=664-777 % |
| Redness ^d | | | |
| Any | 10.8 | 22.2 ^g | 14.3 |
| Mild | 9.5 | 13.5 | 12.6 |
| Moderate | 4.7 | 11.5 ^g | 6.5 |
| Severe | 1.7 | 4.8 ^g | 1.1 |
| Swelling ^d | | | |
| Any | 10.4 | 23.1 ^g | 12.8 |
| Mild | 8.9 | 14.0 ^g | 10.9 |
| Moderate | 4.0 | 13.6 ^g | 5.5 |
| Severe | 0.0 | 4.8 ^g | 0.6 |
| Pain ^e | | | |
| Any | 51.7 | 58.5 | 51.0 |
| Mild | 50.1 | 54.1 | 49.4 |
| Moderate | 7.5 | 23.6 ^g | 9.0 |
| Severe | 1.3 | 2.3 | 0.2 |
| Limitation of arm movement ^f | | | |
| Any | 10.5 | 27.6 ^g | 16.2 |
| Mild | 10.3 | 25.2 ^g | 14.8 |
| Moderate | 0.3 | 2.6 ^g | 1.6 |
| Severe | 0.7 | 3.0^{g} | 1.6 |

^a Study conducted in US and Sweden NCT00546572 (Study 7) reported local reactions within 14 days. Study conducted in US, Sweden and Germany NCT00500266 (Study 9) reported local reactions within 14 days.

^b Open label administration of Prevnar 13.

^c Number of subjects with known values.

^d Diameters were measured in caliper units of whole numbers from 1 to 21 or 21+. One caliper unit = 0.5 cm. Measurements were rounded up to the nearest whole number. Intensity of redness and swelling were then characterized as Mild = 2.5 to 5.0 cm, Moderate = 5.1 to 10.0 cm, and Severe is >10.0 cm.

^e Mild = awareness of symptom but easily tolerated, Moderate = discomfort enough to cause interference with usual activity, Severe = incapacitating with inability to do usual activity.

f Mild = some limitation of arm movement, Moderate = unable to move arm above head but able to move arm above shoulder, and Severe = unable to move arm above shoulder.

^g Statistically significant difference p <0.05. No adjustments for multiplicity.

Table 13 - Percentage of Subjects With Solicited Systemic Events in PPSV23 Unvaccinated Adults^a

| | | Study 6 | | | Study 8 | | Study 12 | | |
|-------------|-------------------------|-------------------------|-----------------|-----------------|------------|-------------------|-------------------|------------|--|
| Age in | 18-49 | 18-49 50-59 60-64 60-64 | | -64 | ≥65 | | | | |
| Years | | | | | | | | | |
| | Prevnar 13 ^b | Prevnar 13 ^b | Prevnar 13 | PPSV23 | Prevnar 13 | PPSV23 | Prevnar 13 | Placebo | |
| | $N^c = 221 - 561$ | N°=137-248 | $N^{c}=174-277$ | $N^{c}=176-273$ | N°=261-328 | N°=127-173 | N°=881-896 | N°=860-878 | |
| | % | % | % | % | % | % | % | % | |
| Systemic | | | | | | | | | |
| Event | | | | | | | | | |
| Fever | | | | | | | | | |
| ≥38.0°C | 7.2 | 1.5 | 4.0 | 1.1 | 4.2 | 1.6 | 2.9 ^d | 1.3 | |
| 38.0°C to | 4.2 | 1.5 | 4.0 | 1.1 | 3.8 | 0.8 | 1.1 | 0.6 | |
| 38.4°C | | 1.3 | 4.0 | 1.1 | 3.6 | 0.8 | | | |
| 38.5°C to | 1.9 | 0.0 | 0.6 | 0.0 | 0.8 | 0.0 | 0.6 | 0.2 | |
| 38.9°C | | 0.0 | 0.0 | 0.0 | 0.8 | 0.0 | | | |
| 39.0°C to | 1.4 | 0.0 | 0.0 | 0.0 | 0.4 | 0.8 | 0.7 | 0.2 | |
| 40.0°C | | 0.0 | 0.0 | 0.0 | 0.4 | 0.8 | | | |
| >40.0°Ce | 0.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.8 | 0.3 | |
| Fatigue | 80.5 | 63.3 | 63.2 | 61.5 | 50.5 | 49.1 | 18.8 ^d | 14.8 | |
| Headache | 81.4 | 65.9 | 54.0 | 54.4 | 49.7 | 46.1 | 15.9 | 14.8 | |
| Chills | 38.1 | 19.6 | 23.5 | 24.1 | 19.9 | 26.9 | 9.4 | 8.4 | |
| Rash | 21.3 | 14.2 | 16.5 | 13.0 | 8.6 | 13.4 | 3.3 ^d | 0.8 | |
| Vomiting | 15.0 | 6.9 | 3.9 | 5.4 | 3.1 | 3.1 | 0.3 | 0.9 | |
| Decreased | 55.6 | 25.2 | 21.2 | 21.7 | 147 | 22 od | 5.3 | 3.7 | |
| appetite | | 25.3 | 21.3 | 21.7 | 14.7 | 23.0 ^d | 3.3 | | |
| Generalized | 82.0 | | | | | | | | |
| new muscle | | 61.8 | 56.2 | 57.8 | 46.9 | 51.5 | 18.4 ^d | 8.4 | |
| pain | | | | | | | | | |
| Generalized | 55.9 | | | | | | | | |
| aggravated | | 39.9 | 32.6 | 37.3 | 22.0 | 32.5 ^d | 9.1 ^d | 4.4 | |
| muscle pain | | | | | | | | | |
| Generalized | 41.7 | | | | | | | | |
| new joint | | 31.5 | 24.4 | 30.1 | 15.5 | 23.8 ^d | 7.4 | 5.4 | |
| pain | | | | | | <u> </u> | | | |
| Generalized | 28.6 | | | | | | | | |
| aggravated | | 25.6 | 24.9 | 21.4 | 14.0 | 21.1 | 5.2 | 4.2 | |
| joint pain | | COO 427005 (Ct1 | | | | <u> </u> | | | |

^a Studies conducted in US NCT00427895 (Study 6) and NCT00574548 (Study 8) reported systemic events within 14 days. Study conducted in the Netherlands NCT00744263 (Study 12) reported systemic events within 7 days.

^b Open label administration of Prevnar 13.

^c Number of subjects with known values (number of subjects reporting yes for at least one day or no for all days).

 $^{^{\}rm d}$ Statistically significant difference p <0.05. No adjustments for multiplicity.

^e Fevers >40.0°C were confirmed to be data entry errors and remain in the table for the following: 1 case in the 18- to 49- year-old cohort (Study 6), and 7 cases in the Prevnar 13 group and 3 cases in placebo group (Study 12). For the other cohorts in Study 6 and for Study 8, data entry errors were removed.

Study 7 Study 9 Age in Years ≥70 ≥68 PPSV23 Prevnar 13 Prevnar 13^b N°=299-350 N°=303-367 $N^{c}=635-733$ % % % Systemic Event Fever ≥38.0°C 1.0 2.3 1.1 38.0°C to 38.4°C 1.0 2.0 0.8 38.5°C to 38.9°C 0.0 0.0 0.0 39.0°C to 40.0°C 0.0 0.3 0.3 >40.0°C 0.0 0.0 0.0 34.0 43.3^d 34.4 Fatigue Headache 23.7 26.0 26.1 Chills 7.9 11.2 7.5 16.4° 8.4 7.3 Rash Vomiting 1.7 1.3 0.9 11.2 Decreased appetite 11.5 44.7^d 36.8 Generalized new muscle pain Generalized aggravated muscle 20.6 27.5^{d} 12.3

Table 14 - Percentage of Subjects With Systemic Events in PPSV23 Previously Vaccinated Adults^a

14.9

16.5

Generalized new joint pain
Generalized aggravated joint

pain

pain

12.6

11.6

Safety Results from Adult Clinical Study of Concomitant Administration of Prevnar 13 and IIV4 (Fluzone Quadrivalent) (Study 13)

The safety profile of Prevnar 13 when administered concomitantly with seasonal inactivated influenza vaccine, quadrivalent, to PPSV23 previously vaccinated adults ≥50 years of age was generally consistent with the known safety profile of Prevnar 13.

6.3 Post-marketing Experience With Prevnar 13 in Infants and Toddlers

The following adverse events have been reported through passive surveillance since market introduction of Prevnar 13. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine. The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Prevnar 13 vaccine.

<u>Administration site conditions</u>: Vaccination-site dermatitis, vaccination-site pruritus, vaccination-site urticaria

<u>Blood and lymphatic system disorders</u>: Lymphadenopathy localized to the region of the injection site

Cardiac disorders: Cyanosis

21

12.8

9.7

^a Study conducted in US and Sweden NCT00546572 (Study 7) reported systemic events within 14 days. Study conducted in US, Sweden and Germany NCT00500266 (Study 9) reported systemic events within 14 days.

^b Open label administration of Prevnar 13.

^c Number of subjects with known values.

d Statistically significant difference p <0.05. No adjustments for multiplicity.

<u>Immune system disorders</u>: Anaphylactic/anaphylactoid reaction including shock

Nervous system disorders: Hypotonia

Skin and subcutaneous tissue disorders: Angioneurotic edema, erythema multiforme

Respiratory: Apnea

<u>Vascular disorders</u>: Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Immunizations

In clinical trials with infants and toddlers, Prevnar 13 was administered concomitantly with the following US-licensed vaccines: Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] (DTaP-HBV-IPV) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)] (PRP-T) for the first three doses and with PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PRP-OMP), M-M-R II [Measles, Mumps, Rubella Virus Vaccine Live] (MMR) and Varivax [Varicella Virus Vaccine Live], or ProQuad [Measles, Mumps, Rubella and Varicella Virus Vaccine Live] (MMRV) and VAQTA [Hepatitis A vaccine, Inactivated] (HepA) for dose 4 [see Clinical Studies (14.2) and Adverse Reactions (6.1)].

In children and adolescents, data are insufficient to assess the concomitant administration of Prevnar 13 with Human Papillomavirus Vaccine (HPV), Meningococcal Conjugate Vaccine (MCV4) and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Tdap).

In adults, Prevnar 13 was administered concomitantly with US-licensed inactivated influenza vaccines, trivalent and quadrivalent (Studies 10, 11 and 13)[see Clinical Studies (14.4) and Adverse Reactions (6.2)]. There are no data on the concomitant administration of Prevnar 13 with diphtheria toxoid-containing vaccines and other vaccines licensed for use in adults 50 years of age and older.

When Prevnar 13 is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

Do not mix Prevnar 13 with other vaccines/products in the same syringe.

7.2 Immunosuppressive Therapies

Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents) may not respond optimally to active immunization.

7.3 Antipyretics

A post-marketing clinical study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13. The data show that 3 doses of acetaminophen (the first dose administered at the time of each vaccination and the subsequent doses at 6 to 8 hour intervals) reduced the antibody response to some serotypes following the third dose of Prevnar 13, compared with responses among infants who received antipyretics only as needed for treatment. Reduced antibody responses were not observed after the fourth dose of Prevnar 13 when acetaminophen was administered prophylactically.

7.4 Prior Vaccination with PPSV23

Prior receipt of PPSV23 within 1 year results in diminished immune responses to Prevnar 13 compared to PPSV23 naïve individuals [see Clinical Studies (14.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on Prevnar 13 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study has been performed in female rabbits administered Prevnar 13 prior to mating and during gestation. Each dose was approximately 20 times the human dose. This study revealed no evidence of harm to the fetus due to Prevnar 13 (*see 8.1 Data*).

Data

Animal

In a developmental toxicity study, female rabbits were administered Prevnar 13 by intramuscular injection twice prior to mating (17 days and 3 days prior to mating) and twice during gestation (gestation days 10 and 24), 0.5 mL/rabbit/occasion (each dose approximately 20 times the human dose). No adverse effects on pre-weaning development were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

Data are not available to assess the effects of Prevnar 13 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Prevnar 13 and any potential adverse effects on the breastfed child from Prevnar 13 or from the underlying maternal condition. For

preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine

8.4 Pediatric Use

Safety and effectiveness of Prevnar 13 in children below the age of 6 weeks have not been established.

8.5 Geriatric Use

Of the total number of Prevnar 13 recipients aged 50 years and older in clinical studies (N=47,907), 94.5% (45,291 of 47,907) were 65 years and older and 30.3 % (14,498 of 47,907) were 75 years and older [see Clinical Studies (14.1) and (14.3)].

8.6 High Risk Populations

Individuals with the diseases or conditions listed below are at increased risk of pneumococcal disease. Immunogenicity and safety data in these populations are limited.

Infants Born Prematurely

Immune responses elicited by Prevnar 13 administered on a US schedule to preterm infants have not been studied. When preterm infants (<37 weeks gestational age, N=100) were administered 4 doses of Prevnar 13 on a non-US schedule, the serotype-specific IgG antibody responses after the third and fourth dose were lower compared to responses among term infants (≥37 weeks gestational age, N=100) for some serotypes; the effectiveness of Prevnar 13 in preterm infants cannot be established from this study.

Children with Sickle Cell Disease

In an open-label, single-arm, descriptive study, 2 doses of Prevnar 13 were administered 6 months apart to children ≥6 to <18 years of age with sickle cell disease who previously received PPSV23 at least 6 months prior to enrollment. Children with a prior history of pneumococcal conjugate vaccination were excluded. For all vaccine serotypes, anti-pneumococcal opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) were higher after the first dose compared to pre-vaccination (N=95-131); OPA GMTs following the first and second dose were comparable. The effectiveness of Prevnar 13 in this specific population has not been established.

Individuals with Hematopoietic Stem Cell Transplant

In an open-label, single-arm, descriptive study, 4 doses of Prevnar 13 were administered to subjects ≥ 2 years of age (range 2 to 71 years) who had received an allogeneic hematopoietic stem cell transplant 3 to 6 months prior to enrollment. All subjects had a history of stable engraftment (absolute neutrophil count>1000/ μ L, platelet count>50,000/ μ L), and did not have uncontrolled graft versus host disease. The first three doses of Prevnar 13 were administered one month apart, followed by a fourth dose of Prevnar 13 six months after the third dose. Sera were obtained approximately one month after each vaccination. Immune responses (IgG GMCs) after the first

dose of Prevnar 13 were numerically higher for all serotypes compared with baseline. In addition, after each subsequent dose of Prevnar 13, IgG GMCs for all serotypes were numerically higher than responses after the previous dose. A post hoc analysis of the immune responses as measured by OPA antibody assay showed the pattern of functional antibody responses to be consistent with IgG responses for each serotype. The effectiveness of Prevnar 13 in this specific population has not been established.

Individuals with HIV Infection

In an open-label, single-arm, descriptive study, 3 doses of Prevnar 13 were administered 6 months apart to HIV-infected adults ≥18 years of age (median age 48 years), with CD4 counts ≥200 cells/µL and serum HIV RNA titer <50,000 copies/mL. All subjects had been vaccinated previously with PPSV23 at least 6 months prior to enrollment. For all vaccine serotypes anti-pneumococcal OPA GMTs were numerically higher after the first dose compared to pre-vaccination (N=227-253); OPA GMTs following the first, second and third dose were generally comparable. The effectiveness of Prevnar 13 in this specific population has not been established.

In an open-label, single-arm, descriptive study, 3 doses of Prevnar 13 were administered 1 month apart to HIV-infected subjects ≥ 6 years of age with CD4 counts ≥ 200 cells/ μ L, and serum HIV RNA titer < 50,000 copies/mL. Subjects had not previously been vaccinated with a pneumococcal vaccine. For all vaccine serotypes anti-pneumococcal OPA GMTs were numerically higher after the first dose compared to pre-vaccination (N=197-257); OPA GMTs following the first, second and third dose were generally comparable. The effectiveness of Prevnar 13 in this specific population has not been established.

11 DESCRIPTION

Prevnar 13, Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein) is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually linked to non-toxic diphtheria CRM₁₉₇ protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides, which are directly conjugated by reductive amination to the protein carrier CRM₁₉₇, to form the glycoconjugate. CRM₁₉₇ is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium or in a chemically-defined medium. CRM₁₉₇ is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

The individual glycoconjugates are compounded to formulate Prevnar 13. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens and by the saccharide to protein ratios in the individual glycoconjugates. Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 µg of each of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg of 6B saccharides, 34 µg

CRM197 carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer and 125 µg aluminum as aluminum phosphate adjuvant.

The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Prevnar 13, comprised of pneumococcal polysaccharides conjugated to a carrier protein (CRM₁₉₇), elicits a T-cell dependent immune response. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response.

Nonclinical and clinical data support opsonophagocytic activity, as measured by opsonophagocytic activity (OPA) antibody assay, as a contributor to protection against pneumococcal disease. The OPA antibody assay provides an in vitro measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant in vivo mechanisms of protection against pneumococcal disease. OPA antibody titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%.

In infants that have received Prevnar 13, opsonophagocytic activity correlates well with serotype specific anti-capsular polysaccharide IgG levels as measured by ELISA. A serum anti-capsular polysaccharide antibody concentration of $0.35~\mu g/mL$ as measured by ELISA one month after the third dose as a single antibody reference concentration was used to estimate the effectiveness of Prevnar 13 against invasive pneumococcal disease (IPD) in infants and children. The assay used for this determination is a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. The single antibody reference value was based on pooled efficacy estimates from three placebo-controlled IPD efficacy trials with either Prevnar or the investigational 9-valent CRM₁₉₇ conjugate pneumococcal polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis. Functional antibodies elicited by the vaccine (as measured by a dribble opsonophagocytic activity [dOPA] antibody assay) were also evaluated in infants.

In adults, an antipolysaccharide binding antibody IgG level to predict protection against invasive pneumococcal disease or non-bacteremic pneumonia has not been defined. Noninferiority trials for Prevnar 13 were designed to show that functional OPA antibody responses (as measured by a microcolony OPA [mcOPA] antibody assay) for the Prevnar 13 serotypes are noninferior and for some serotypes superior to the common serotypes in the currently licensed pneumococcal polysaccharide vaccine (PPSV23). OPA antibody titers measured in the mcOPA antibody assay cannot be compared directly to titers measured in the dOPA antibody assay.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Prevnar 13 has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a study in rabbits, no vaccine-related effects were found regarding reproductive performance including female fertility [see Use in Specific Populations (8.1)].

14 CLINICAL STUDIES

14.1 Efficacy Data

Prevnar Efficacy Data

Invasive Pneumococcal Disease (IPD)

Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM·197 Protein]) was licensed in the US for infants and children in 2000, following a randomized, double-blind clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either Prevnar or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-15 months of age. In this study, the efficacy of Prevnar against invasive disease due to *S. pneumoniae* in cases accrued during this period was 100% in both the per-protocol and intent-to-treat analyses (95% confidence interval [CI]: 75.4%, 100% and 81.7%, 100%, respectively). Data accumulated through an extended follow-up period to April 20, 1999, resulted in similar efficacy estimates of 97.4% in the per-protocol analysis and 93.9% in the intent-to-treat analysis (95% CI: 82.7%, 99.9% and 79.6%, 98.5%, respectively).

Acute Otitis Media (AOM)

The efficacy of Prevnar against otitis media was assessed in two clinical trials: a trial in Finnish infants at the National Public Health Institute and the efficacy trial in US infants at Northern California Kaiser Permanente (NCKP).

The Finnish Otitis Media (FinOM) trial was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either Prevnar or a control vaccine Recombivax HB (Hepatitis B vaccine (Recombinant) [Hep B]) at 2, 4, 6, and 12-15 months of age. In this study, conducted between December 1995 and March 1999, parents of study participants were asked to bring their children to the study clinics if the child had respiratory infections or symptoms suggesting acute otitis media (AOM). If AOM was diagnosed, tympanocentesis was performed, and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed; the primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per-protocol population. In the NCKP trial, the efficacy of Prevnar against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to receive either Prevnar (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis

media was used by study physicians. The primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population.

The vaccine efficacy against AOM episodes due to vaccine serotypes assessed in the Finnish trial, was 57% (95% CI: 44%, 67%) in the per-protocol population and 54% (95% CI: 41%, 64%) in the intent-to-treat population. The vaccine efficacy against AOM episodes due to vaccine-related serotypes (6A, 9N, 18B, 19A, 23A), also assessed in the Finnish trial, was 51% (95% CI: 27, 67) in the per-protocol population and 44% (95% CI: 20, 62) in the intent-to-treat population. There was a nonsignificant increase in AOM episodes caused by serotypes unrelated to the vaccine in the per-protocol population, compared to children who received the control vaccine, suggesting that children who received Prevnar appeared to be at increased risk of otitis media due to pneumococcal serotypes not represented in the vaccine. However, vaccination with Prevnar reduced pneumococcal otitis media episodes overall. In the NCKP trial, in which the endpoint was all otitis media episodes regardless of etiology, vaccine efficacy was 7% (95% CI: 4%, 10%) and 6% (95% CI: 4%, 9%), respectively, in the per-protocol and intent-to-treat analyses. Several other otitis media endpoints were also assessed in the two trials.

Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% in both the per-protocol and intent-to-treat populations (95% CI: 3%, 15% in per-protocol and 95% CI: 4%, 14% in intent-to-treat) in the NCKP trial; a similar trend was observed in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI: 2, 35) in the placement of tympanostomy tubes in the per-protocol population and a 21% reduction (95% CI: 4, 34) in the intent-to-treat population. Data from the NCKP trial accumulated through an extended follow-up period to April 20, 1999, in which a total of 37,866 children were included (18,925 in Prevnar group and 18,941 in MnCC control group), resulted in similar otitis media efficacy estimates for all endpoints.

Prevnar 13 Adult Efficacy Data

The efficacy of Prevnar 13 against vaccine-type (VT) pneumococcal community-acquired pneumonia (CAP) and IPD was assessed in a randomized, double-blind, placebo-controlled study conducted over ~ 4 years in the Netherlands (Study 12). A total of 84,496 subjects 65 years and older received a single dose of either Prevnar 13 or placebo in a 1:1 randomization; 42,240 subjects were vaccinated with Prevnar 13 and 42,256 subjects were vaccinated with placebo.

The primary objective was to demonstrate the efficacy of Prevnar 13 in the prevention of a first episode of confirmed VT-CAP (defined as presence of ≥2 specified clinical criteria; chest X-ray consistent with CAP as determined by a central committee of radiologists; and positive VT-specific Urinary Antigen Detection assay (UAD) or isolation of VT S. pneumoniae from blood or other sterile site). The secondary objectives were to demonstrate the efficacy of Prevnar 13 in the prevention of a first episode of 1) confirmed nonbacteremic/noninvasive (NB/NI) VT-CAP (an episode of VT-CAP for which the blood culture result and any other sterile site culture results were negative for S. pneumoniae) and 2) VT-IPD (the presence of *S. pneumoniae* in a sterile site).

Surveillance for suspected pneumonia and IPD began immediately after vaccination and continued through identification of a prespecified number of cases. Subjects who had a CAP or IPD episode with symptom onset less than 14 days after vaccination were excluded from all analyses.

The median duration of follow-up per subject was 3.93 years. Prevnar 13 demonstrated statistically significant vaccine efficacy (VE) in preventing first episodes of VT pneumococcal CAP, nonbacteremic/noninvasive (NB/NI) VT pneumococcal CAP, and VT-IPD (Table 15).

| | | Vaccine C | roup | | |
|--|-----------------------------|------------|---------|-----------|--------------|
| | | Prevnar 13 | Placebo | | |
| | | N=42240 | N=42256 | | |
| Efficacy Endpoint | Total Number of Episodes | n | n | VE (%) | (95.2% CI) |
| Primary endpoint: First case of confirmed VT pneumococcal CAP | 139 | 49 | 90 | 45.6 | (21.8, 62.5) |
| Secondary endpoint: First episode of confirmed NB/NI VT pneumococcal CAP | 93 | 33 | 60 | 45 | (14.2, 65.3) |
| Secondary endpoint: First episode of VT-IPD | 35 | 7 | 28 | 75 | (41.1, 90.9) |

Table 15 - Vaccine Efficacy for the Primary and Secondary Efficacy Endpoints - Per-Protocol Population

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; NB/NI = nonbacteremic/noninvasive; IPD = invasive pneumococcal disease; VE = vaccine efficacy; VT = vaccine-type.

14.2 Prevnar 13 Clinical Trials in Children 6 Weeks Through 17 Years of Age Infants and Children 6 Weeks Through 17 Months of Age

Prevnar 13 effectiveness against invasive pneumococcal disease was inferred from comparative studies to a US-licensed 7-valent pneumococcal conjugate vaccine, Prevnar, in which Prevnar 13 elicited antipolysaccharide binding and functional OPA antibodies, as measured by ELISA and dOPA assays, respectively. These studies were designed to evaluate immunologic noninferiority of Prevnar 13 to Prevnar.

Clinical trials have been conducted in the US using a 2, 4, 6, and 12-15 month schedule.

The US noninferiority study² (Study 2) was a randomized, double-blind, active-controlled trial in which 2 month-old infants were randomly assigned to receive either Prevnar 13 or Prevnar in a 1:1 ratio. The two vaccine groups were well balanced with respect to race, ethnicity, and age and weight at enrollment. Most subjects were White (69.1%), 19.6% were Black or African-American, and 2.4% were Asian; 82.1% of subjects were non-Hispanic and non-Latino and 17.3% were Hispanic or Latino. Overall, 54.0% of subjects were male infants.

In Study 2, immune responses were compared in subjects receiving either Prevnar 13 or Prevnar using a set of noninferiority criteria. Co-primary endpoints included the percentage of subjects with serum pneumococcal anti-capsular polysaccharide $IgG \ge 0.35 \mu g/mL$ measured one month

after the third dose and serum pneumococcal anti-capsular polysaccharide IgG geometric mean concentrations (GMCs) one month after the fourth dose. The assay used for this determination was a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity. Responses to the 7 common serotypes in Prevnar 13 and Prevnar recipients were compared directly. Responses to the 6 additional serotypes in Prevnar 13 recipients were each compared to the lowest response observed among the Prevnar serotypes in Prevnar recipients.

Pneumococcal Immune Responses Following Three Doses

In Study 2, the noninferiority criterion for the proportion of subjects with pneumococcal anti-capsular polysaccharide IgG antibody concentrations $\geq 0.35~\mu g/mL$ one month after the third dose was met for 10 of the 13 serotypes. The exceptions were serotypes 6B, 9V, and 3. Although the response to serotypes 6B and 9V did not meet the pre-specified noninferiority criterion, the differences were marginal.

The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations \geq 0.35 µg/mL one month after the third dose is shown below (Table 16).

Table 16: Percentage of Subjects With Anti-capsular Antibody Concentration ≥0.35 μg/mL One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2^{a,b,c,d}

| Serotype | Prevnar 13 | Prevnar | Difference in % responders |
|----------|-------------------|-----------------------------------|----------------------------|
| | N=249-252 | N=250-252 | (95% CI) |
| | (95% CI) | (95% CI) | |
| | | Prevnar Serotypes | |
| 4 | 94.4 (90.9, 96.9) | 98.0 (95.4, 99.4) | -3.6 (-7.3, -0.1) |
| 6B | 87.3 (82.5, 91.1) | 92.8 (88.9, 95.7) | -5.5 (-10.9, -0.1) |
| 9V | 90.5 (86.2, 93.8) | 98.4 (96.0, 99.6) | -7.9 (-12.4, -4.0) |
| 14 | 97.6 (94.9, 99.1) | 97.2 (94.4, 98.9) | 0.4 (-2.7, 3.5) |
| 18C | 96.8 (93.8, 98.6) | 98.4 (96.0, 99.6) | -1.6 (-4.7, 1.2) |
| 19F | 98.0 (95.4, 99.4) | 97.6 (99.4, 99.1) | 0.4 (-2.4, 3.4) |
| 23F | 90.5 (86.2, 93.8) | 94.0 (90.4, 96.6) | -3.6 (-8.5, 1.2) |
| | | Additional Serotypes ^e | |
| 1 | 95.6 (92.3, 97.8) | e | 2.8 (-1.3, 7.2) |
| 3 | 63.5 (57.1, 69.4) | e | -29.3 (-36.2, -22.4) |
| 5 | 89.7 (85.2, 93.1) | e | -3.1 (-8.3, 1.9) |
| 6A | 96.0 (92.8, 98.1) | e | 3.2 (-0.8, 7.6) |
| 7F | 98.4 (96.0, 99.6) | e | 5.6 (1.9, 9.7) |
| 19A | 98.4 (96.0, 99.6) | e | 5.6 (1.9, 9.7) |

^a Studies conducted in US NCT00373958 (Study 2).

^b Evaluable Immunogenicity Population.

c Noninferiority was met when the lower limit of the 95% CI for the difference between groups (Prevnar 13 minus Prevnar) was greater than -10%

^d Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.

^e Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which for this analysis was serotype 6B (92.8%; 95% CI: 88.9, 95.7).

Functional dOPA antibody responses were elicited for all 13 serotypes, as shown in Table 17.

Table 17: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After a Three Dose Series Administered at 2, 4 and 6 Months of Age, Study 2^{a,b,c}

| Serotype | Prevnar 13 | Prev | nar | |
|----------|----------------------|---------|--------------|--|
| | N=91-94 | N=89-94 | | |
| | (95% CI) | (95% | 6 CI) | |
| | Prevnar Serotypes | | | |
| 4 | 359 (276, 468) | 536 | (421, 681) | |
| 6B | 1055 (817, 1361) | 1514 | (1207, 1899) | |
| 9V | 4035 (2933, 5553) | 3259 | (2288, 4641) | |
| 14 | 1240 (935, 1646) | 1481 | (1133, 1934) | |
| 18C | 276 (210, 361) | 376 | (292, 484) | |
| 19F | 54 (40, 74) | 45 | (34, 60) | |
| 23F | 791 (605, 1034) | 924 | (709, 1204) | |
| | Additional Serotypes | | | |
| 1 | 52 (39, 69) | 4 | (4, 5) | |
| 3 | 121 (92, 158) | 7 | (5, 9) | |
| 5 | 91 (67, 123) | 4 | (4, 4) | |
| 6A | 980 (783, 1226) | 100 | (66, 152) | |
| 7F | 9494 (7339, 12281) | 128 | (80, 206) | |
| 19A | 152 (105, 220) | 7 | (5, 9) | |

^a Studies conducted in US NCT00373958 (Study 2).

Pneumococcal Immune Responses Following Four Doses

In Study 2, post-dose 4 antibody concentrations were higher for all 13 serotypes than those achieved after the third dose. The noninferiority criterion for pneumococcal anti-capsular polysaccharide GMCs after 4 doses was met for 12 of the 13 pneumococcal serotypes. The noninferiority criterion was not met for the response to serotype 3 (Table 18).

Table 18: Pneumococcal IgG GMCs (µg/mL) One Month After a Four Dose Series Administered at 2, 4, 6 and 12-15 Months, Study 2abe, at

| Serotype | Prevnar 13 | Prevnar | GMC Ratio |
|----------|---------------------|-----------------------------------|-------------------|
| | N=232-236 | N=222-223 | (95% CI) |
| | (95% CI) | (95% CI) | |
| | | Prevnar Serotypes | |
| 4 | 3.73 (3.28, 4.24) | 5.49 (4.91, 6.13) | 0.68 (0.57, 0.80) |
| 6B | 11.53 (9.99, 13.30) | 15.63 (13.80, 17.69) | 0.74 (0.61, 0.89) |
| 9V | 2.62 (2.34, 2.94) | 3.63 (3.25, 4.05) | 0.72 (0.62, 0.85) |
| 14 | 9.11 (7.95, 10.45) | 12.72 (11.22, 14.41) | 0.72 (0.60, 0.86) |
| 18C | 3.20 (2.82, 3.64) | 4.70 (4.18, 5.28) | 0.68 (0.57, 0.81) |
| 19F | 6.60 (5.85, 7.44) | 5.60 (4.87, 6.43) | 1.18 (0.98, 1.41) |
| 23F | 5.07 (4.41, 5.83) | 7.84 (6.91, 8.90) | 0.65 (0.54, 0.78) |
| | | Additional Serotypes ^e | |
| 1 | 5.06 (4.43, 5.80) | e | 1.40 (1.17, 1.66) |
| 3 | 0.94 (0.83, 1.05) | e | 0.26 (0.22, 0.30) |
| 5 | 3.72 (3.31, 4.18) | e | 1.03 (0.87, 1.20) |
| 6A | 8.20 (7.30, 9.20) | e | 2.26 (1.93, 2.65) |
| 7F | 5.67 (5.01, 6.42) | e | 1.56 (1.32, 1.85) |
| 19A | 8.55 (7.64, 9.56) | e | 2.36 (2.01, 2.76) |

^a Studies conducted in US NCT00373958 (Study 2).

^b The dOPA (opsonophagocytic activity) antibody assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.

^c Evaluable Immunogenicity Population.

^b Evaluable Immunogenicity Population.

^c Noninferiority was declared if the lower limit of the 2-sided 95% CI for Geometric Mean Ratio (Prevnar 13:Prevnar) was greater than 0.5.

^d Antibody measured by a standardized ELISA involving pre-absorption of the test sera with pneumococcal C-polysaccharide and serotype 22F polysaccharide to reduce non-specific background reactivity.

^e Comparison for the 6 additional serotypes was to the lowest responder of the 7 common serotypes in Prevnar recipients, which for this analysis was serotype 9V (3.63; 95% CI 3.25, 4.05).

Following the fourth dose, the functional dOPA antibody response for each serotype was quantitatively greater than the response following the third dose (see Table 19).

Table 19: Pneumococcal dOPA Antibody Geometric Mean Titers One Month After the Fourth Dose-Evaluable Toddler Immunogenicity Population, Study 2^{a,b}

| Serotype | | Prevnar 13 | | Prevnar |
|----------|-------|------------------|-------|----------------|
| | | N=88-92 | | N=92-96 |
| | | (95% CI) | | (95% CI) |
| | | Prevnar Seroty | pes | |
| 4 | 1180 | (847, 1643) | 1492 | (1114, 1999) |
| 6B | 3100 | (2337, 4111) | 4066 | (3243, 5098) |
| 9V | 11856 | (8810, 15955) | 18032 | (14125, 23021) |
| 14 | 2002 | (1453, 2760) | 2366 | (1871, 2992) |
| 18C | 993 | (754, 1308) | 1722 | (1327, 2236) |
| 19F | 200 | (144, 276) | 167 | (121, 230) |
| 23F | 2723 | (1961, 3782) | 4982 | (3886, 6387) |
| <u>.</u> | | Additional Serot | ypes | |
| 1 | 164 | (114, 237) | 5 | (4, 6) |
| 3 | 380 | (300, 482) | 12 | (9, 16) |
| 5 | 300 | (229, 393) | 5 | (4, 6) |
| 6A | 2242 | (1707, 2945) | 539 | (375, 774) |
| 7F | 11629 | (9054, 14938) | 268 | (164, 436) |
| 19A | 1024 | (774, 1355) | 29 | (19, 44) |

^a Studies conducted in US NCT00373958 (Study 2).

Previously Unvaccinated Older Infants and Children 7 Months Through 5 Years of Age

In an open-label descriptive study of Prevnar 13 in Poland⁴ (Study 4), children 7 months through 11 months of age, 12 months through 23 months of age and 24 months through 5 years of age (prior to the 6th birthday) who were naïve to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of Prevnar 13 respectively, according to the age-appropriate schedules in Table 2. Serum IgG concentrations were measured one month after the final dose in each age group and the data are shown in Table 20.

Table 20: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (μg/mL) One Month After the Final Prevnar 13 Catch-Up Dose in Pneumococcal Vaccine Naïve Children 7 Months Through 5 Years of Age by Age Group, Study 4^{a,b}

| Serotype | 3 doses Prevnar 13 7 through 11 months | 2 doses Prevnar 13 12 through 23 months | 1 dose Prevnar 13 24 months through 5 years |
|----------|---|--|--|
| | N=83-84 | N=104-110 | N=135-152 |
| | (95% CI) | (95% CI) | (95% CI) |
| 1 | 2.88 (2.44, 3.39) | 2.74 (2.37, 3.16) | 1.78 (1.52, 2.08) |
| 3 | 1.94 (1.68, 2.24) | 1.86 (1.60, 2.15) | 1.42 (1.23, 1.64) |
| 4 | 3.63 (3.11, 4.23) | 4.28 (3.78, 4.86) | 3.37 (2.95, 3.85) |
| 5 | 2.85 (2.34, 3.46) | 2.16 (1.89, 2.47) | 2.33 (2.05, 2.64) |
| 6A | 3.72 (3.12, 4.45) | 2.62 (2.25, 3.06) | 2.96 (2.52, 3.47) |
| 6B | 4.77 (3.90, 5.84) | 3.38 (2.81, 4.06) | 3.41 (2.80, 4.16) |
| 7F | 5.30 (4.54, 6.18) | 5.99 (5.40, 6.65) | 4.92 (4.26, 5.68) |
| 9V | 2.56 (2.21, 2.96) | 3.08 (2.69, 3.53) | 2.67 (2.32, 3.07) |
| 14 | 8.04 (6.95, 9.30) | 6.45 (5.48, 7.59) | 2.24 (1.71, 2.93) |
| 18C | 2.77 (2.39, 3.23) | 3.71 (3.29, 4.19) | 2.56 (2.17, 3.03) |
| 19A | 4.77 (4.28, 5.33) | 4.94 (4.31, 5.65) | 6.03 (5.22, 6.97) |
| 19F | 2.88 (2.35, 3.54) | 3.07 (2.68, 3.51) | 2.53 (2.14, 2.99) |
| 23F | 2.16 (1.82, 2.55) | 1.98 (1.64, 2.39) | 1.55 (1.31, 1.85) |

^a Studies conducted in Poland NCT00452452 (Study 4).

^b The dOPA (opsonophagocytic activity) antibody assay measures the ability of immune sera, in conjunction with complement, to mediate the uptake and killing of *S. pneumoniae* by phagocytic cells.

^bOpen label administration of Prevnar 13.

Note - ClinicalTrials.gov NCT number is as follows: NCT00452452 (Poland).

Children 15 Months Through 59 Months of Age Previously Vaccinated with Prevnar

In an open-label descriptive study in the US⁵ (Study 5), children 15 months through 59 months previously vaccinated with 3 or 4 doses of Prevnar, received 2 doses of Prevnar 13 (children >15 through 23 months of age) or 1 dose of Prevnar 13 (children 24 months through 59 months of age). The data following one dose of Prevnar 13 in children 24 months through 59 months of age are shown in Table 21.

Table 21: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (μg/mL) One Month After One Prevnar 13 Catch-Up Dose in Children 24 Through 59 Months of Age With 3 or 4 Prior Doses of Prevnar, US Catch-Up Study 5^{a,b}

| Serotype | 1 dose Prevnar 13 |
|---|-----------------------------|
| | 24 months through 59 months |
| | N=173-175 |
| | (95% CI) |
| 1 | 2.43 (2.15, 2.75) |
| 3 | 1.38 (1.17, 1.61) |
| 5 | 2.13 (1.89, 2.41) |
| 6A | 12.96 (11.04, 15.21) |
| 7F | 4.22 (3.74, 4.77) |
| 19A | 14.18 (12.37, 16.25) |
| ^a Studies conducted in US NCT00761631 (Study | 75). |
| ^b Open label administration of Prevnar 13. | |

Children 5 Through 17 Years of Age

In a US study⁵ (Study 5), a single dose of Prevnar 13 was administered to children 5 through 9 years of age, who were previously vaccinated with at least one dose of Prevnar, and to pneumococcal vaccine-naïve children 10 through 17 years of age.

In children 5 through 9 years of age, serotype-specific IgG concentrations measured 1 month after vaccination were noninferior (i.e., the lower limit of the 2-sided 95% CI for the geometric mean ratio [GMR] of >0.5) to the corresponding IgG concentrations in toddlers (Study 3) 1 month after a fourth pneumococcal vaccination (after the 4th dose of Prevnar for the 7 common serotypes and after the 4th dose of Prevnar 13 for the 6 additional serotypes) as shown in Tables 22 and 23 respectively.

Table 22: Pneumococcal IgG GMCs (µg/mL) One Month After Vaccination for 7 Common Serotypes, Prevnar 13 in Children 5 through 9 Years of Age in Study 5 Relative to Prevnar in Study 3 (Post-toddler) agd

| | | Prevnar 13 5 Through 9 Years (Study 5) | | | Prevnar Post-Toddler Dose (Study 3) | | | | |
|----------|--|--|----------------|----------------|---|------------------------|---------------------------|------------------------|--|
| Serotype | n ^b GMC ^c (95% CI ^d) | | | n ^b | GMC° | (95% CI ^d) | GMC Ratio ^e | (95% CI ^f) | |
| Common | | | | | | | | | |
| 4 | 169 | 8.45 | (7.24, 9.87) | 173 | 2.79 | (2.45, 3.18) | 3.03 | (2.48, 3.71) | |
| 6B | 171 | 53.56 | (45.48, 63.07) | 173 | 9.47 | (8.26, 10.86) | 5.66 | (4.57, 6.99) | |
| 9V | 171 | 9.51 | (8.38, 10.78) | 172 | 1.97 | (1.77, 2.19) | 4.83 | (4.10, 5.70) | |
| 14 | 169 | 29.36 | (24.78, 34.78) | 173 | 8.19 | (7.31, 9.18) | 3.58 | (2.93, 4.39) | |
| 18C | 171 | 8.23 | (7.13, 9.51) | 173 | 2.33 | (2.05, 2.65) | 3.53 | (2.91, 4.29) | |
| 19F | 171 | 17.58 | (14.95, 20.67) | 173 | 3.31 | (2.87, 3.81) | 5.31 | (4.29, 6.58) | |
| 23F | 169 | 11.26 | (9.79, 12.95) | 173 | 4.49 | (3.86, 5.23) | 2.51 | (2.04, 3.08) | |

^a Studies conducted in US NCT00761631 (Study 5) and NCT00444457 (Study 3).

Table 23: Pneumococcal IgG GMCs (µg/mL) One Month After Vaccination for Additional 6 Serotypes, Prevnar 13 in Children 5 through 9 Years of Age in Study 5 Relative to Prevnar 13 in Study 3 (Post-toddler)^{a,g,h}

| | Prevnar 13 5 Through 9 Years (Study 5) | | | Prevnar 13 Post-Toddler Dose (Study 3) | | | | |
|------------|--|-------|------------------------|--|------------------|------------------------|---------------------------|------------------------|
| Serotype | erotype n ^b | | (95% CI ^d) | n ^b | GMC ^c | (95% CI ^d) | GMC Ratio ^e | (95% CI ^f) |
| Additional | | | | | | | | |
| 1 | 171 | 3.57 | (3.05, 4.18) | 1068 | 2.90 | (2.75, 3.05) | 1.23 | (1.07, 1.42) |
| 3 | 171 | 2.38 | (2.07, 2.74) | 1065 | 0.75 | (0.72, 0.79) | 3.17 | (2.78, 3.62) |
| 5 | 171 | 5.52 | (4.82, 6.32) | 1068 | 2.85 | (2.72, 2.98) | 1.94 | (1.71, 2.20) |
| 6A | 169 | 21.51 | (18.15, 25.51) | 1063 | 7.11 | (6.78, 7.46) | 3.03 | (2.64, 3.47) |
| 7F | 170 | 6.24 | (5.49, 7.08) | 1067 | 4.39 | (4.18, 4.61) | 1.42 | (1.24, 1.62) |
| 19A | 170 | 17.18 | (15.01, 19.67) | 1056 | 8.44 | (8.05, 8.86) | 2.03 | (1.78, 2.32) |

^a Studies conducted in US NCT00761631 (Study 5) and NCT00444457 (Study 3).

In children 10 through 17 years of age OPA GMTs, as measured by the mcOPA assay, 1 month after vaccination were noninferior (i.e., the lower limit of the 2-sided 95% CI for the GMR of

^b n = Number of subjects with a determinate antibody concentration for the specified serotype.

^c Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after a 4-dose vaccination series with Prevnar (Study 3, post-toddler).

^d Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the

e Ratio of GMCs: Prevnar 13 (Study 5) to Prevnar (Study 3) reference.

^f CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13 (Study 5) – Prevnar (Study 3)].

^g Evaluable Immunogenicity Population.

h Noninferiority was declared if the lower limit of the 2-sided 95% CI for geometric mean ratio was greater than 0.5.

^b n = Number of subjects with a determinate antibody concentration for the specified serotype.

⁶ Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMC after a 4-dose vaccination series with Prevnar 13 (Study 3, post-toddler).

d Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations

^e Ratio of GMCs: Prevnar 13 (Study 5) to Prevnar 13 (Study 3).

f CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13 (Study 5) – Prevnar 13 (Study 3)].

^g Evaluable Immunogenicity Population.

^h Noninferiority was declared if the lower limit of the 2-sided 95% CI for geometric mean ratio was greater than 0.5.

>0.5) to mcOPA GMTs in the 5 through 9 year old group for 12 of 13 serotypes (except for serotype 3), as shown in Table 24.

Table 24: Comparison of Pneumococcal mcOPA GMTs One Month After Vaccination, Prevnar 13, in Children 10 through 17 Years of Age Relative to Prevnar 13 in Children 5 through 9 Years of Age ag,h,i

| | Prevnar 13 (10 through 17 Years) | | | | Prevnar 13 (5 through 9 Years) | | | |
|------------|-------------------------------------|------------------|------------------------|----------------|-----------------------------------|------------------------|---------------------------|------------------------|
| Serotype | n ^b | GMT ^c | (95% CI ^d) | n ^b | GMT ^c | (95% CI ^d) | GMT Ratio ^e | (95% CI ^f) |
| Common | | | | | | | | |
| 4 | 188 | 6912 | (6101, 7831) | 181 | 4629 | (4017, 5334) | 1.5 | (1.24, 1.80) |
| 6B | 183 | 14224 | (12316, 16427) | 178 | 14996 | (13164, 17083) | 0.9 | (0.78, 1.15) |
| 9V | 186 | 4485 | (4001, 5028) | 180 | 4733 | (4203, 5328) | 0.9 | (0.80, 1.12) |
| 14 | 187 | 6894 | (6028, 7884) | 176 | 4759 | (4120, 5497) | 1.4 | (1.19, 1.76) |
| 18C | 182 | 6263 | (5436, 7215) | 175 | 8815 | (7738, 10041) | 0.7 | (0.59, 0.86) |
| 19F | 184 | 2280 | (1949, 2668) | 178 | 1591 | (1336, 1893) | 1.4 | (1.14, 1.81) |
| 23F | 187 | 3808 | (3355, 4323) | 176 | 3245 | (2819, 3736) | 1.2 | (0.97, 1.42) |
| Additional | | | | | | | | |
| 1 | 189 | 322 | (275, 378) | 179 | 191 | (165, 221) | 1.7 | (1.36, 2.10) |
| 3 | 181 | 114 | (101, 130) | 178 | 203 | (182, 226) | 0.6 | (0.48, 0.67) |
| 5 | 183 | 360 | (298, 436) | 178 | 498 | (437, 568) | 0.7 | (0.57, 0.91) |
| 6A | 182 | 9928 | (8457, 11655) | 178 | 7514 | (6351, 8891) | 1.3 | (1.05, 1.67) |
| 7F | 185 | 6584 | (5829, 7436) | 178 | 10334 | (9099, 11737) | 0.6 | (0.53, 0.76) |
| 19A | 187 | 1276 | (1132, 1439) | 180 | 1180 | (1048, 1329) | 1.1 | (0.91, 1.28) |

^a Studies conducted in US NCT00761631 (Study 5).

14.3 Prevnar 13 Immunogenicity Clinical Trials in Adults

Six Phase 3 or Phase 4 clinical trials^{6-8,10,11,13} were conducted in the US and Europe evaluating the immunogenicity of Prevnar 13 in different adult age groups, in individuals who were either not previously vaccinated with PPSV23 (PPSV23 unvaccinated) or who had received one dose of PPSV23 (PPSV23 previously vaccinated).

Each study included healthy adults and immunocompetent adults with stable underlying conditions including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease, and medical risk conditions and behaviors (e.g., alcoholism and smoking) that are known to increase the risk of serious pneumococcal pneumonia and invasive pneumococcal disease. A stable medical condition was defined as a medical condition not requiring significant change in therapy (i.e., change to new therapy category due to worsening disease) or hospitalization for worsening disease 6-12 weeks prior to receipt of the study vaccine.

^b n= Number of subjects with a determinate antibody titer for the specified serotype.

^c Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.

d Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

^e Ratio of GMTs: Prevnar 13(10 through 17 years of age) to Prevnar 13 (5 through 9 years of age).

^f CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13(10 through 17 years of age) – Prevnar 13(5 through 9 years of age)] Study 5.

g Evaluable Immunogenicity Population.

h Noninferiority was declared if the lower limit of the 2-sided 95% CI for geometric mean ratio was greater than 0.5.

individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.

Immune responses elicited by Prevnar 13 and PPSV23 were measured by a mcOPA antibody assay for the 13 pneumococcal serotypes contained in Prevnar 13. Serotype-specific mcOPA antibody GMTs measured 1 month after each vaccination were calculated. For the 12 serotypes in common to both vaccines, noninferiority between vaccines was met if the lower limit of the 2-sided 95% confidence interval (CI) of the GMT ratio (Prevnar 13/PPSV23) was greater than 0.5.

The response to the additional serotype 6A, which is contained in Prevnar 13 but not in PPSV23, was assessed by demonstration of a \geq 4-fold increase in the anti-6A mcOPA antibody titer above preimmunization levels. A statistically significantly greater response for Prevnar 13 was defined, for the difference in percentages (Prevnar 13 minus PPSV23) of adults achieving a \geq 4-fold increase in anti-6A mcOPA antibody titer, as the lower limit of the 2-sided 95% CI greater than zero. For comparison of mcOPA antibody GMTs, a statistically greater response for serotype 6A was defined as the lower limit of the 2-sided 95% CI of the GMT ratio (Prevnar 13/PPSV23) greater than 2.

Of the 6 Phase 3 or Phase 4 clinical trials, 2 noninferiority trials^{6,7} were conducted in which the immune responses to Prevnar 13 were compared with the immune responses to PPSV23; one in PPSV23 unvaccinated adults aged 18 through 64 years⁶ (Study 6), and one in PPSV23 previously vaccinated adults aged ≥70 years⁷ (Study 7). A third study compared immune responses to a single dose of Prevnar 13 to the response to Prevnar 13 administered one year after a dose of PPSV23 in adults aged 60 through 64 years who were PPSV23 unvaccinated at enrollment⁸ (Study 8). The study also compared immune responses of PPSV23 as a single dose to the responses to PPSV23 administered one year after a dose of Prevnar 13. Two studies assessed the concomitant administration of Prevnar 13 with seasonal inactivated Fluarix (IIV3) in the US¹⁰ (Study 10) and Europe¹¹ (Study 11). One study (Study 13) assessed the concomitant administration of Prevnar 13 with seasonal inactivated Fluzone Quadrivalent (IIV4) in PPSV23 previously vaccinated adults ≥50 years of age in the US.

Overall across the clinical studies evaluating the immunogenicity of Prevnar 13 in adults, persons 18 through 64 years of age responded at least as well as persons 65 years and older, the age group evaluated in a clinical endpoint efficacy trial.

Clinical Trials Conducted in PPSV23 Unvaccinated Adults

In an active-controlled modified^a double-blind clinical trial⁶ (Study 6) of Prevnar 13 in the US, PPSV23 unvaccinated adults aged 60 through 64 years were randomly assigned (1:1) to receive Prevnar 13 or PPSV23. In addition, adults aged 18 through 49 years and 50 through 59 years were enrolled and received one dose of Prevnar 13 (open-label).

^a Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.

In adults aged 60 through 64 years, the mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines (see Table 24). In addition, the lower limit of the 95% confidence interval for the mcOPA antibody GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 8 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a ≥4-fold increase after Prevnar 13 (88.5%) was statistically significantly greater than after PPSV23 (49.3%) in PPSV23-unvaccinated adults aged 60 through 64 years. OPA antibody GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23 (see Table 25).

The mcOPA antibody GMTs elicited by Prevnar 13 in adults aged 50 through 59 years were noninferior to the corresponding mcOPA antibody GMTs elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 25).

In adults aged 18 through 49 years, the mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by Prevnar 13 in adults aged 60 through 64 years for all 13 serotypes (see Table 25).

Table 25: mcOPA Antibody GMTs in PPSV23-Unvaccinated Adults Aged 18 Through 49 Years or Aged 50 Through 59 Years Given Prevnar 13 and in Adults Aged 60 Through 64 Years Given Prevnar 13 or PPSV23 (Study 6)^{a,b,c,d,e}

| | Prevnar 13 | Prevnar 13 | Prevnar 13 | PPSV23 | Prevnar 13 18-49 Relative to 60-64 Years | Prevnar 13 50-59 Relative to 60-64 Years | Prevnar 13 Relative to PPSV23, 60-64 Years ^g |
|-----------------|------------|------------|------------|-----------|--|--|---|
| | N=836-866 | N=350-384 | N=359-404 | N=367-402 | | | |
| Serotype | GMT | GMT | GMT | GMT | GMT Ratio (95% CI) | GMT Ratio (95% CI) | GMT Ratio (95% CI) |
| 1 | 353 | 211 | 158 | 119 | 2.4 | 1.3 | 1.3 |
| | 91 | | | | (2.03, 2.87) | (1.07, 1.65) 1.0 | (1.07, 1.65) |
| 3 | 91 | 94 | 96 | 90 | (0.84, 1.13) | (0.82, 1.18) | (0.89, 1.29) |
| 4 | 4747 | 2904 | 2164 | 1405 | (0.84, 1.13) 2.3 (1.92, 2.76) 1.9 | (0.82, 1.18) 1.3 (1.06, 1.70) 1.4 | (0.89, 1.29) 1.5 (1.18, 2.00) |
| 5 | 386 | 322 | 236 | 198 | 1.9 (1.55, 2.42) 2.2 | 1.4 (1.08, 1.74) 1.6 | 1.2 (0.95, 1.50) |
| 6A ^h | 5746 | 4469 | 2766 | 343 | 2.2 (1.84, 2.67) 4.9 | 1.6 (1.28, 2.03) 1.5 | 8.1 (6.11, 10.67) 2.2 |
| 6B | 9813 | 3350 | 2212 | 998 | 4.9 (4.13, 5.93) 2.9 | 1.5 (1.20, 1.91) 1.2 | 2.2 (1.70, 2.89) 1.9 |
| 7F | 3249 | 1807 | 1535 | 829 | 2.9 (2.41, 3.49) 2.9 | 1.2 (0.98, 1.41) 1.3 | 1.9 (1.52, 2.26) 1.7 |
| 9V | 3339 | 2190 | 1701 | 1012 | 2.9 (2.34, 3.52) 4.9 | 1.3 (1.08, 1.53) | 1.7 (1.40, 2.02) 0.9 |
| 14 | 2983 | 1078 | 733 | 819 | 4.9 (4.01, 5.93) 2.3 | | |
| 18C | 3989 | 2077 | 1834 | 1074 | 2.3 (1.91, 2.79) | 1.1 (0.89, 1.44) 1.4 | (0.69, 1.16) 1.7 (1.32, 2.21) |
| 19A | 1580 | 968 | 691 | 368 | | 1.4 (1.17, 1.68) 1.1 | |
| 19F | 1533 | 697 | 622 | 636 | 3.0 (2.44, 3.60) 4.2 | | 1.0 (0.78, 1.23) 4.6 |
| 23F | 1570 | 531 | 404 | 87 | 4.2 (3.31, 5.31) | 1.3 (0.96, 1.80) | 4.6 (3.37, 6.38) |

GMT. Geometric Mean Titer.

Clinical Trials Conducted in PPSV23 Previously Vaccinated Adults

In a Phase 3 active-controlled, modified double-blind clinical trial (Study 7) of Prevnar 13 in the US and Sweden, PPSV23 previously vaccinated adults aged \geq 70 years who had received one dose of PPSV23 \geq 5 years prior were randomly assigned (1:1) to receive either Prevnar 13 or PPSV23.

^a Study conducted in US NCT00427895 (Study 6).

^b Noninferiority was defined for the 13 serotypes in adults aged 18 to 49 years, for the 12 common serotypes in adults aged 60 to 64 years and for the 13 serotypes in adults aged 50 to 59 years as the lower limit of the 2-sided 95% CI for GMT ratio greater than 0.5.

^c mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.

^d Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.

^e Evaluable Immunogenicity Population.

^fOpen label administration of Prevnar 13.

^g For serotype 6A, which is unique to Prevnar 13, a statistically significantly greater response was defined for analysis in cohort 1 as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13/PPSV23) greater than 2.

¹6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

The mcOPA antibody GMTs elicited by Prevnar 13 were noninferior to those elicited by PPSV23 for the 12 serotypes in common, when Prevnar 13 or PPSV23 were administered at a minimum of 5 years after a prior dose of PPSV23. In addition, the lower limit of the 95% confidence interval for the mcOPA antibody GMT ratio (Prevnar 13/PPSV23) was greater than 1 for 9 of the serotypes in common.

For serotype 6A, which is unique to Prevnar 13, the proportion of subjects with a ≥4-fold increase in mcOPA antibody titers after Prevnar 13 (71.1%) was statistically significantly greater than after PPSV23 (27.3%) in PPSV23 previously vaccinated adults aged ≥70 years. mcOPA antibody GMTs for serotype 6A were statistically significantly greater after Prevnar 13 compared with after PPSV23.

This clinical trial demonstrated that in adults aged ≥70 years and previously vaccinated with PPSV23 ≥5 years prior, vaccination with Prevnar 13 elicited noninferior immune responses as compared with re-vaccination with PPSV23 (see Table 26).

Table 26: mcOPA Antibody GMTs in PPSV23-Previously Vaccinated Adults Aged ≥70 Years Given Prevnar 13 or PPSV23 (Study 7)^{a,b,c,d,e,f}

| Serotype | Prevnar 13 N=400-426 | PPSV23 N=395-445 | Prevnar 13 Relative to PPSV23 | | |
|-----------------|--------------------------------|----------------------------|----------------------------------|--------------|--|
| | GMT | GMT | GMT Ratio | (95% CI) | |
| 1 | 93 | 66 | 1.4 | (1.14, 1.72) | |
| 3 | 59 | 53 | 1.1 | (0.92, 1.31) | |
| 4 | 613 | 263 | 2.3 | (1.76, 3.10) | |
| 5 | 100 | 61 | 1.6 | (1.35, 2.00) | |
| 6A ^g | 1056 | 160 | 6.6 | (5.14, 8.49) | |
| 6B | 1450 | 565 | 2.6 | (2.00, 3.29) | |
| 7F | 559 | 481 | 1.2 | (0.97, 1.39) | |
| 9V | 622 | 491 | 1.3 | (1.08, 1.49) | |
| 14 | 355 | 366 | 1.0 | (0.76, 1.23) | |
| 18C | 972 | 573 | 1.7 | (1.33, 2.16) | |
| 19A | 366 | 216 | 1.7 | (1.40, 2.07) | |
| 19F | 422 | 295 | 1.4 | (1.16, 1.77) | |
| 23F | 177 | 53 | 3.3 | (2.49, 4.47) | |

GMT, Geometric Mean Titer.

Clinical Trial of Sequential Vaccination of Prevnar 13 and PPSV23 in PPSV23 Unvaccinated Adults

In a randomized clinical trial conducted in PPSV23-unvaccinated adults 60 through 64 years of age⁸ (Study 8), 223 subjects received PPSV23 followed by Prevnar 13 one year later (PPSV23/Prevnar 13), and 478 received only Prevnar 13. mcOPA antibody titers were measured 1 month after vaccination with Prevnar 13 and are shown in Table 26. mcOPA antibody GMTs in those that received Prevnar 13 one year after PPSV23 were diminished when compared to those who received Prevnar 13 alone. Similarly, in exploratory analyses in PPSV23 previously

^a Study conducted in US and Sweden NCT00546572 (Study 7).

^b For the 12 common serotypes, noninferiority was defined as the lower limit of the 2-sided 95% CI for GMT ratio (Prevnar 13/PPSV23) greater than 0.5.

^c For serotype 6A, which is unique to Prevnar 13, a statistically significantly greater response was defined as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13/PPSV23) greater than 2.

^d mcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.

e Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.

^f Evaluable Immunogenicity Population.

^g 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

vaccinated adults ≥70 years of age in Study 7, diminished mcOPA antibody GMTs were observed in those that received Prevnar 13 one year after PPSV23 when compared to those who received Prevnar 13 alone.

Table 27: mcOPA Antibody GMTs for the Prevnar 13 Serotypes in PPSV23 Unvaccinated Adults Aged 60 Through 64 Years Given Prevnar 13 Alone or Prevnar 13 One Year After PPSV23 (Study 8) (PPSV23/Prevnar 13)^{a,b,c,d}

| | | Prevnar 13 N=410-457 | PPSV23/Prevnar 13 N=180-196 | | |
|-----------------|------|-------------------------|--------------------------------|-------------|--|
| Serotype | GMT | (95% CI) | GMT | (95% CI) | |
| 1 | 219 | (191, 252) | 88 | (72, 109) | |
| 3 | 78 | (69, 88) | 54 | (45, 65) | |
| 4 | 2590 | (2257, 2973) | 988 | (802, 1218) | |
| 5 | 258 | (218, 305) | 112 | (90, 139) | |
| 6A ^e | 2947 | (2536, 3426) | 1210 | (962, 1522) | |
| 6B | 2165 | (1845, 2540) | 832 | (654, 1059) | |
| 7F | 1518 | (1339, 1721) | 407 | (342, 485) | |
| 9V | 1279 | (1142, 1432) | 495 | (426, 575) | |
| 14 | 790 | (663, 941) | 515 | (402, 659) | |
| 18C | 1683 | (1437, 1971) | 650 | (504, 839) | |
| 19A | 717 | (629, 818) | 299 | (248, 361) | |
| 19F | 812 | (702, 939) | 360 | (293, 442) | |
| 23F | 384 | (312, 472) | 142 | (104, 193) | |

GMT =Geometric Mean Titer.

Also in Study 8, 266 subjects received Prevnar 13 followed by PPSV23 one year later (Prevnar 13/PPSV23). mcOPA antibody GMTs following PPSV23 administered one year after Prevnar 13 (Prevnar 13/PPSV23) were noninferior to those following a single dose of PPSV23 (N=237) for the 12 common serotypes [the lower limit of the 95% CI for the GMT ratio [Prevnar 13/PPSV23 relative to PPSV23] was >0.5] (see Table 27). In Study 6, which was conducted in PPSV23-unvaccinated adults 60 through 64 years of age, 108 subjects received PPSV23 3.5 to 4 years after Prevnar 13 (Prevnar 13/PPSV23) and 414 received a single dose of PPSV23. Higher serotype-specific mcOPA antibody GMT ratios [(Prevnar 13/PPSV23) / PPSV23] were generally observed compared to the one year dosing interval in Study 8.

^a Study conducted in US NCT00574548 (Study 8).

^b Evaluable Immunogenicity Population.

^cmcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.

^d Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.

^e 6A is a serotype unique to Prevnar 13 but not contained in PPSV23

Table 28: mcOPA Antibody GMTs for the Prevnar 13 Serotypes in PPSV23-Unvaccinated Adults Aged 60 Through 64 Years Given PPSV23 One Year After Prevnar 13 Relative to PPSV23 Alone (Study 8)^{a,b,c,d}

| | Prevnar 13/PPSV23 N=216-233 | | | PPSV23 I=214-229 | GMT Ratio (Prevnar 13/PPSV23) / PPSV23 | | |
|-----------------|--------------------------------|--------------|------|---------------------|---|--------------|--|
| Serotype | GMT | 95% CI | GMT | 95% CI | Ratio | 95% CI | |
| 1 | 155 | (131, 182) | 161 | (131, 198) | 1.0 | (0.74, 1.25) | |
| 3 | 127 | (111, 145) | 83 | (71, 98) | 1.5 | (1.23, 1.87) | |
| 4 | 1409 | (1202, 1651) | 1468 | (1139, 1893) | 1.0 | (0.71, 1.29) | |
| 5 | 220 | (184, 264) | 178 | (144, 222) | 1.2 | (0.93, 1.64) | |
| 6A ^e | 1366 | (1122, 1663) | 400 | (306, 524) | 3.4 | (2.45, 4.77) | |
| 6B | 1345 | (1113, 1625) | 875 | (689, 1111) | 1.5 | (1.14, 2.08) | |
| 7F | 748 | (653, 857) | 719 | (598, 865) | 1.0 | (0.83, 1.31) | |
| 9V | 848 | (731, 984) | 824 | (694, 977) | 1.0 | (0.82, 1.29) | |
| 14 | 711 | (580, 872) | 869 | (677, 1115) | 0.8 | (0.59, 1.13) | |
| 18C | 1115 | (925, 1344) | 912 | (707, 1177) | 1.2 | (0.89, 1.67) | |
| 19A | 471 | (408, 543) | 390 | (318, 477) | 1.2 | (0.94, 1.55) | |
| 19F | 819 | (697, 963) | 626 | (504, 779) | 1.3 | (1.00, 1.71) | |
| 23F | 216 | (169, 277) | 84 | (62, 114) | 2.6 | (1.74, 3.79) | |

GMT =Geometric Mean Titer.

14.4 Concomitant Vaccine Administration

Infants and Toddlers

The concomitant administration of routine US infant vaccines [see Drug Interactions (7.1)] with Prevnar 13 was evaluated in two studies: Study 2 [see Clinical Studies (14.2)], Pneumococcal Immune Responses Following Three Doses², and the US lot consistency study³ (Study 3). In Study 3, subjects were randomly assigned to receive one of 3 lots of Prevnar 13 or Prevnar in a 2:2:2:1 ratio. The total number of infants vaccinated was 663² (Study 2) and 1699³ (Study 3). Immune responses to concomitant vaccine antigens were compared in infants receiving Prevnar and Prevnar 13. Responses to diphtheria toxoid, tetanus toxoid, pertussis, polio types 1, 2, and 3, hepatitis B, PRP-T, PRP-OMP, measles, and varicella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients. Based on limited data, responses to mumps and rubella antigens in Prevnar 13 recipients were similar to those in Prevnar recipients.

Adults ≥50 Years of Age

Concomitant Administration with QIV

Prevnar 13 was administered to PPSV23 previously vaccinated adults ≥50 years of age concomitantly with a US-licensed inactivated influenza vaccine, quadrivalent (IIV4) (Fluzone Quadrivalent) for the 2014/2015 influenza season (Study 13) [see Adverse Reactions (6.2) and Drug Interactions (7.1)]. One study group received Prevnar 13 and IIV4 concurrently, followed approximately one month later by placebo. A second study group received IIV4 and placebo concurrently, followed approximately one month later by Prevnar 13.

Serotype-specific pneumococcal antibody responses were measured one month after Prevnar 13 vaccination as OPA GMTs. Noninferiority was demonstrated for each pneumococcal serotype if the lower limit of the 2-sided 95% CI for the GMT ratio (Prevnar 13 + IIV4 relative to Prevnar

^a Study conducted in US NCT00574548 (Study 8).

^bEvaluable Immunogenicity Population.

^cmcOPA antibody for the 11 serotypes unique to PPSV23 but not contained in Prevnar 13 were not measured.

^d Individual mcOPA antibody assay values below the assay LLOQ (lower limit of quantitation) were set at 0.50*LLOQ for the purpose of calculating the mcOPA antibody GMT.

^e 6A is a serotype unique to Prevnar 13 but not contained in PPSV23. Anti-6A mcOPA antibody GMTs were descriptive in nature.

13 alone) was >0.5. Although OPA antibody responses to Prevnar 13 generally appeared to be slightly lower when Prevnar 13 was administered concomitantly with IIV4 compared to Prevnar 13 administered alone, noninferiority was demonstrated for all Prevnar 13 pneumococcal serotypes evaluated in Study 13.

Strain-specific influenza antibody responses were measured one month after IIV4 as hemagglutinin inhibition assay (HAI) titers. HAI GMTs were evaluated for each IIV4 strain in Study 13. Noninferiority was demonstrated if the lower limit of the 2-sided 95% CI for the HAI GMT ratio (Prevnar 13 + IIV4 relative to IIV4 + Placebo) was >0.5. Noninferiority was demonstrated for each IIV4 vaccine strain evaluated in Study 13.

Concomitant Administration with TIV

Two randomized, double-blind clinical trials evaluated the immunogenicity of Prevnar 13 given with IIV3 (Fall 2007/ Spring 2008 Fluarix, A/H1N1, A/H3N2, and B strains) in PPSV23 unvaccinated adults aged 50 through 59 years ¹⁰ (Study 10, conducted in the US) and in adults ≥65 years ¹¹ (Study 11, conducted in Europe). Based on analysis of the primary pre-specified comparison of serotype specific anti-capsular polysaccharide IgG GMCs, noninferiority was met for all serotypes in adults 50-59 years of age and for 12 of 13 serotypes in adults ≥65 years of age.

15 REFERENCES

ClinicalTrials.gov identifiers for studies included below:

- 1. Study 1 NCT00205803
- 2. Study 2 NCT00373958
- 3. Study 3 NCT00444457
- 4. Study 4 NCT00452452
- 5. Study 5 NCT00761631
- 6. Study 6 NCT00427895
- 7. Study 7 NCT00546572
- 8. Study 8 NCT00574548
- 9. Study 9 NCT00500266
- 10. Study 10 NCT00521586
- 11. Study 11 NCT00492557
- 12. Study 12 NCT00744263
- 13. Study 13 NCT02124161

16 HOW SUPPLIED/STORAGE AND HANDLING

Prefilled Syringe, 1 Dose (10 per package) – NDC 0005-1971-02.

Prefilled Syringe, 1 Dose (1 per package) – NDC 0005-1971-05.

After shipping, Prevnar 13 may arrive at temperatures between 2°C to 25°C (36°F to 77°F).

Upon receipt, store refrigerated at 2°C to 8°C (36°F to 46°F).

Do not freeze. Discard if the vaccine has been frozen.

Prevnar 13 is stable at temperatures up to 25°C (77°F) for 4 days. These data are not recommendations for shipping or storage, but may guide decisions for use in case of temporary temperature excursions.

The tip cap and rubber plunger of the prefilled syringe are not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Prior to administration of this vaccine, inform the individual, parent, guardian, or other responsible adult of the following:

- The potential benefits and risks of immunization with Prevnar 13 [see Warnings and Precautions (5) and Adverse Reactions (6)].
- The importance of completing the immunization series unless contraindicated.
- Any suspected adverse reactions should be reported to their healthcare professional.

Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.



US Govt. License No. 3

LAB-0469-17.0 CPT Code 90670

EXHIBIT 244

1 AHFS Category: 80:12

Poliovirus Vaccine Inactivated IPOL®



IPV

2 DESCRIPTION

- 3 IPOL®, Poliovirus Vaccine Inactivated, produced by Sanofi Pasteur SA, is a sterile suspension of
- 4 three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). IPOL
- 5 vaccine is a highly purified, inactivated poliovirus vaccine with enhanced potency. Each of the
- 6 three strains of poliovirus is individually grown in vero cells, a continuous line of monkey kidney
- 7 cells cultivated on microcarriers. (1) (2) The cells are grown in Eagle MEM modified medium,
- 8 supplemented with newborn calf bovine serum tested for adventitious agents prior to use,
- 9 originated from countries free of bovine spongiform encephalopathy. For viral growth, the culture
- medium is replaced by M-199, without calf bovine serum. This culture technique and
- improvements in purification, concentration, and standardization of poliovirus antigen produce a
- more potent and consistent immunogenic vaccine than the inactivated poliovirus vaccine (IPV)
- available in the US prior to 1988. (3) (4)

- 15 After clarification and filtration, viral suspensions are concentrated by ultrafiltration, and purified
- by three liquid chromatography steps; one column of anion exchanger, one column of gel
- 17 filtration, and again one column of anion exchanger. After re-equilibration of the purified viral
- suspension with Medium M-199 and adjustment of the antigen titer, the monovalent viral
- suspensions are inactivated at +37°C for at least 12 days with 1:4000 formalin.

1 2 Each dose (0.5 mL) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D 3 antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus. For each lot of IPOL 4 vaccine, D-antigen content is determined in vitro using the D-antigen ELISA assay. IPOL vaccine is produced from vaccine concentrates diluted with M-199 medium. Also present are 0.5% of 2-5 6 phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, 7 streptomycin, and polymyxin B are used in vaccine production; and, although purification 8 procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin, and 25 9 ng polymyxin B per dose may still be present. The residual calf bovine serum albumin is less than 10 50 ng/dose in the final vaccine. 11 12 The vaccine is clear and colorless and should be administered intramuscularly or subcutaneously. 13 14 The vial and vial stopper are not made with natural rubber latex. 15 CLINICAL PHARMACOLOGY 16 17 Poliomyelitis is caused by poliovirus Types 1, 2, or 3. It is primarily spread by the fecal-oral route 18 of transmission but may also be spread by the pharyngeal route. 19 20 Approximately 90% to 95% of poliovirus infections are asymptomatic. Nonspecific illness with 21 low-grade fever and sore throat (minor illness) occurs in 4% to 8% of infections. Aseptic 22 meningitis occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid 23 onset of asymmetric acute flaccid paralysis occurs in 0.1% to 2% of infections, and residual

1 paralytic disease involving motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 2 1,000 infections. (5) 3 4 Prior to the introduction of inactivated poliovirus vaccines in 1955, large outbreaks of 5 poliomyelitis occurred each year in the United States (US). The annual incidence of paralytic 6 disease of 11.4 cases/100,000 population declined to 0.5 cases by the time oral poliovirus vaccine 7 (OPV) was introduced in 1961. Incidence continued to decline thereafter to a rate of 0.002 to 8 0.005 cases per 100,000 population. Of the 127 cases of paralytic poliomyelitis reported in the US 9 between 1980 and 1994, six were imported cases (caused by wild polioviruses), two were 10 "indeterminate" cases, and 119 were vaccine associated paralytic poliomyelitis (VAPP) cases 11 associated with the use of live, attenuated oral poliovirus vaccine (OPV). (6) An all IPV schedule 12 was adopted in 1999 to eliminate VAPP cases. (7) 13 14 Poliovirus Vaccine Inactivated induces the production of neutralizing antibodies against each type 15 of virus which are related to protective efficacy. Antibody response in most children was induced 16 after receiving fewer doses (8) of IPV vaccine than the vaccine available in the United States prior 17 to 1988. 18 19 Studies in developed (8) and developing (9), (10) countries with a similar enhanced IPV 20 manufactured by the same process as IPOL vaccine in primary monkey kidney cells have shown a 21 direct relationship exists between the antigenic content of the vaccine, the frequency of 22 seroconversion, and resulting antibody titer. Approval in the US was based upon demonstration of 23 immunogenicity and safety in US children. (11)

1 2 In the US, 219 infants received three doses of a similar enhanced IPV at two, four, and eighteen 3 months of age manufactured by the same process as IPOL vaccine except the cell substrate for 4 IPV was using primary monkey kidney cells. Seroconversion to all three types of poliovirus was 5 demonstrated in 99% of these infants after two doses of vaccine given at 2 and 4 months of age. 6 Following the third dose of vaccine at 18 months of age, neutralizing antibodies were present at a 7 level of ≥1:10 in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses. 8 (3) 9 10 IPOL vaccine was administered to more than 700 infants between 2 to 18 months of age during 11 three clinical studies conducted in the US using IPV only schedules and sequential IPV-OPV 12 schedules. (12) (13) Seroprevalence rates for detectable serum neutralizing antibody (DA) at a 13 ≥1:4 dilution were 95% to 100% (Type 1); 97% to 100% (Type 2) and 96% to 100% (Type 3) 14 after two doses of IPOL vaccine depending on studies. 15 16

1 Table 1: US Studies with IPOL Vaccine Administered Using IPV Only or Sequential IPV-

2 **OPV Schedules**

| Age (months) for | | | Post Dose 2 | | | Post Dose 3 | | | Pre Booster | | | Post Booster | | | | | | | |
|------------------|-------------------|--------|-------------|-----|--------|-------------|--------|----------|-------------|--------|----------|--------------|------|----------|--------|-----|-------|--------|--------|
| 2 | 4 | 6 | 12 to 18 | | Type 1 | Type 2 | Type 3 | | Type 1 | Type 2 | 2 Type 3 | 7 | Гуре | 1 Type 2 | Type 3 | Т | ype 1 | Гуре 2 | Type 3 |
| Dose 1 | Dose 2 | Dose 3 | Booster | N* | %DA** | %DA | %DA | N* | %DA | %DA | %DA | N* % | 6DA | %DA | %DA | N* | %DA | %DA | %DA |
| STUD | Y 1 ⁽¹ | 1)¶ | | | | | | | | | | | | | | | | | |
| I(s) | I(s) | NA† | I(s) | 56 | 97 | 100 | 97 | | _ | _ | _ | 53 | 91 | 97 | 93 | 53 | 97 | 100 | 100 |
| o | O | NA | 0 | 22 | 100 | 100 | 100 | | _ | _ | _ | 22 | 78 | 91 | 78 | 20 | 100 | 100 | 100 |
| I(s) | O | NA | O | 17 | 95 | 100 | 95 | | _ | _ | _ | 17 | 95 | 100 | 95 | 17 | 100 | 100 | 100 |
| I(s) | I(s) | NA | О | 17 | 100 | 100 | 100 | | _ | _ | - | 16 | 100 | 100 | 94 | 16 | 100 | 100 | 100 |
| STUD | Y 2 (1 | 0) § | | | | | | | | | | | | | | | | | |
| I(c) | I(c) | NA | I(s) | 94 | 98 | 97 | 96 | | _ | _ | _ | 100 | 92 | 95 | 88 | 97 | 100 | 100 | 100 |
| I(s) | I(s) | NA | I(s) | 68 | 99 | 100 | 99 | | _ | - | _ | 72 | 100 | 100 | 94 | 75 | 100 | 100 | 100 |
| I(c) | I(c) | NA | O | 75 | 95 | 99 | 96 | | _ | _ | _ | 77 | 86 | 97 | 82 | 78 | 100 | 100 | 97 |
| I(s) | I(s) | NA | О | 101 | 99 | 99 | 95 | | _ | _ | _ | 103 | 99 | 97 | 89 | 107 | 100 | 100 | 100 |
| STUD | Y 3 (1 | 0) § | | | | | | | | | | | | | | | | | |
| I(c) | I(c) | I(c) | О | 91 | 98 | 99 | 100 | 91 | 100 | 100 | 100 | 41 | 100 | 100 | 100 | 40 | 100 | 100 | 100 |
| I(c) | I(c) | О | O | 96 | 100 | 98 | 99 | 94 | 100 | 100 | 99 | 47 | 100 | 100 | 100 | 45 | 100 | 100 | 100 |
| I(c) | I(c) | I(c) + | 00 | 91 | 96 | 97 | 100 | 85 | 100 | 100 | 100 | 47 | 100 | 100 | 100 | 46 | 100 | 100 | 100 |
| * | NT N | т 1 | er of child | 1 | C | 1 | | <u> </u> | 11 1 1 | | | <u> </u> | | | | | | | |

^{3 *} N = Number of children from whom serum was available

- 4 ** Detectable antibody (neutralizing titer ≥1:4)
- 5 † NA No poliovirus vaccine administered
- 6 ¶ IPOL vaccine given subcutaneously
- 7 § IPOL vaccine given intramuscularly
- 8 I IPOL vaccine given either separately in association with DTP in two sites (s) or combined (c) with DTP in a
- 9 dual chambered syringe
- 10 O OPV

1 In one study, (13) the persistence of DA in infants receiving two doses of IPOL vaccine at 2 and 4 2 months of age was 91% to 100% (Type 1), 97% to 100% (Type 2), and 93% to 94% (Type 3) at 3 twelve months of age. In another study, (12) 86% to 100% (Type 1), 95% to 100% (Type 2), and 4 82% to 94% (Type 3) of infants still had DA at 18 months of age. 5 6 In trials and field studies conducted outside the US, IPOL vaccine, or a combination vaccine 7 containing IPOL vaccine and DTP, was administered to more than 3,000 infants between 2 to 18 8 months of age using IPV only schedules and immunogenicity data are available from 1,485 9 infants. After two doses of vaccine given during the first year of life, seroprevalence rates for 10 detectable serum neutralizing antibody (neutralizing titer ≥1:4) were 88% to 100% (Type 1); 84% 11 to 100% (Type 2) and 94% to 100% (Type 3) of infants, depending on studies. When three doses 12 were given during the first year of life, post-dose 3 DA ranged between 93% to 100% (Type 1); 13 89% to 100% (Type 2) and 97% to 100% (Type 3) and reached 100% for Types 1, 2, and 3 after 14 the fourth dose given during the second year of life (12 to 18 months of age). (14) 15 16 In infants immunized with three doses of an unlicensed combination vaccine containing IPOL 17 vaccine and DTP given during the first year of life, and a fourth dose given during the second year 18 of life, the persistence of detectable neutralizing antibodies was 96%, 96%, and 97% against 19 poliovirus Types 1, 2, and 3, respectively, at six years of age. DA reached 100% for all types after 20 a booster dose of IPOL vaccine combined with DTP vaccine. (11) A survey of Swedish children 21 and young adults given a Swedish IPV only schedule demonstrated persistence of detectable 22 serum neutralizing antibody for at least 10 years to all three types of poliovirus. (15)

23

- 1 IPV is able to induce secretory antibody (IgA) produced in the pharynx and gut and reduces
- 2 pharyngeal excretion of poliovirus Type 1 from 75% in children with neutralizing antibodies at
- 3 levels less than 1:8 to 25% in children with neutralizing antibodies at levels more than 1:64. (4)
- 4 (14) (16) (17) (18) (19) (20) (21) (22) There is also evidence of induction of herd immunity with
- 5 IPV, (15) (23) (24) (25) (26) and that this herd immunity is sufficiently maintained in a population
- 6 vaccinated only with IPV. (26)
- 8 VAPP has not been reported in association with administration of IPOL vaccine. (27) It is
- 9 expected that an IPV only schedule will eliminate the risk of VAPP in both recipients and
- 10 contacts compared to a schedule that included OPV. (7)

INDICATIONS AND USAGE

- 13 IPOL vaccine is indicated for active immunization of infants (as young as 6 weeks of age),
- children, and adults for the prevention of poliomyelitis caused by poliovirus Types 1, 2, and 3.
- 15 (28)

7

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17

INFANTS, CHILDREN AND ADOLESCENTS

- 18 General Recommendations
- 19 It is recommended that all infants (as young as 6 weeks of age), unimmunized children, and
- adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.
- 21 (29) Following the eradication of poliomyelitis caused by wild poliovirus from the Western
- Hemisphere (including North and South America) (30), an IPV-only schedule was recommended
- 23 to eliminate VAPP. (7)

1 2 All children should receive four doses of IPV at ages 2, 4, 6 to 18 months, and 4 to 6 years. OPV 3 is no longer available in the US and is not recommended for routine immunization. (7) 4 5 Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete 6 immunization with OPV are not contraindications to completing the primary series of 7 immunization with IPOL vaccine. 8 9 **Children Incompletely Immunized** 10 Children of all ages should have their immunization status reviewed and be considered for 11 supplemental immunization as follows for adults. Time intervals between doses longer than those 12 recommended for routine primary immunization do not necessitate additional doses as long as a 13 final total of four doses is reached (see **DOSAGE AND ADMINISTRATION** section). 14 15 **ADULTS** 16 **General Recommendations** 17 Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) 18 residing in the US is not recommended. Unimmunized adults who are potentially exposed to wild 19 poliovirus and have not been adequately immunized should receive polio vaccination in 20 accordance with the schedule given in the **DOSAGE AND ADMINISTRATION** section. (28) 21 22 Persons with previous wild poliovirus disease who are incompletely immunized or unimmunized 23 should be given additional doses of IPOL vaccine if they fall into one or more categories listed.

1 2 The following categories of adults are at an increased risk of exposure to wild polioviruses: (28) 3 (31)4 • Travelers to regions or countries where poliomyelitis is endemic or epidemic. 5 • Healthcare workers in close contact with patients who may be excreting polioviruses. 6 • Laboratory workers handling specimens that may contain polioviruses. 7 Members of communities or specific population groups with disease caused by wild 8 polioviruses. 9 10 IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS 11 IPOL vaccine should be used in all patients with immunodeficiency diseases and members of 12 such patients' households when vaccination of such persons is indicated. This includes patients 13 with asymptomatic HIV infection, AIDS or AIDS-Related Complex, severe combined 14 immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due 15 to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system 16 compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. 17 Immunogenicity of IPOL vaccine in individuals receiving immunoglobulin could be impaired, 18 and patients with an altered immune state may or may not develop a protective response against 19 paralytic poliomyelitis after administration of IPV. (32) 20 21 As with any vaccine, vaccination with IPOL vaccine may not protect 100% of individuals. 22

1 Use with other vaccines: refer to **DOSAGE AND ADMINISTRATION** section for this 2 information. 3 CONTRAINDICATIONS 4 5 IPOL vaccine is contraindicated in persons with a history of hypersensitivity to any component of 6 the vaccine, including 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, and polymyxin 7 B. 8 9 No further doses should be given if anaphylaxis or anaphylactic shock occurs within 24 hours of 10 administration of one dose of vaccine. 11 12 Vaccination of persons with an acute, febrile illness should be deferred until after recovery; 13 however, minor illness, such as mild upper respiratory infection, with or without low grade fever, 14 are not reasons for postponing vaccine administration. 15 WARNINGS 16 17 Neomycin, streptomycin, polymyxin B, 2-phenoxyethanol, and formaldehyde are used in the 18 production of this vaccine. Although purification procedures eliminate measurable amounts of 19 these substances, traces may be present (see **DESCRIPTION** section), and allergic reactions may 20 occur in persons sensitive to these substances (see **CONTRAINDICATIONS** section). 21

1 Systemic adverse reactions reported in infants receiving IPV concomitantly at separate sites or 2 combined with DTP have been similar to those associated with administration of DTP alone. (11) 3 Local reactions are usually mild and transient in nature. 4 5 Although no causal relationship between IPOL vaccine and Guillain-Barré Syndrome (GBS) has 6 been established, (28) GBS has been temporally related to administration of another inactivated 7 poliovirus vaccine. Deaths have been reported in temporal association with the administration of 8 IPV (see **ADVERSE REACTIONS** section). 9 **PRECAUTIONS** 10 11 **GENERAL** 12 Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse 13 reactions. This includes a review of the patient's history with respect to possible sensitivity to the 14 vaccine or similar vaccines. 15 16 Healthcare providers should question the patient, parent or guardian about reactions to a previous 17 dose of this product, or similar product. 18 19 Epinephrine injection (1:1000) and other appropriate agents should be available to control 20 immediate allergic reactions. 21 22 Healthcare providers should obtain the previous immunization history of the vaccinee, and inquire 23 about the current health status of the vaccinee.

1 2 Immunodeficient patients or patients under immunosuppressive therapy may not develop a 3 protective immune response against paralytic poliomyelitis after administration of IPV. 4 5 Administration of IPOL vaccine is not contraindicated in individuals infected with HIV. (33) (34) 6 (35)7 8 Special care should be taken to ensure that the injection does not enter a blood vessel. 9 INFORMATION FOR PATIENTS 10 11 Patients, parents, or guardians should be instructed to report any serious adverse reactions to their 12 healthcare provider. 13 14 The healthcare provider should inform the patient, parent, or guardian of the benefits and risks of 15 the vaccine. 16 17 The healthcare provider should inform the patient, parent, or guardian of the importance of 18 completing the immunization series. 19 20 The healthcare provider should provide the Vaccine Information Statements (VISs) which are 21 required to be given with each immunization. 22 DRUG INTERACTIONS 23

1 There are no known interactions of IPOL vaccine with drugs or foods. Concomitant 2 administration of other parenteral vaccines, with separate syringes at separate sites, is not 3 contraindicated. The first two doses of IPOL vaccine may be administered at separate sites using 4 separate syringes concomitantly with DTaP, acellular pertussis, *Haemophilus influenzae* type b 5 (Hib), and hepatitis B vaccines. From historical data on the antibody responses to diphtheria, 6 tetanus, acellular pertussis, Hib, or hepatitis B vaccines used concomitantly or in combination 7 with IPOL vaccine, no interferences have been observed on the immunological end points 8 accepted for clinical protection. (11) (16) (36) (See DOSAGE AND ADMINISTRATION 9 section.) 10 11 If IPOL vaccine has been administered to persons receiving immunosuppressive therapy, an 12 adequate immunologic response may not be obtained. (See PRECAUTIONS – GENERAL 13 section.) 14 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY 15 16 Long-term studies in animals to evaluate carcinogenic potential or impairment of fertility have not 17 been conducted. 18 **PREGNANCY** 19 20 Animal reproduction studies have not been conducted with IPOL vaccine. It is also not known 21 whether IPOL vaccine can cause fetal harm when administered to a pregnant woman or can affect 22 reproduction capacity. IPOL vaccine should be given to a pregnant woman only if clearly needed. 23

NURSING MOTHERS

- 2 It is not known whether IPOL vaccine is excreted in human milk. Because many drugs are
- 3 excreted in human milk, caution should be exercised when IPOL vaccine is administered to a
- 4 nursing woman.

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PEDIATRIC USE

- 7 SAFETY AND EFFECTIVENESS OF IPOL VACCINE IN INFANTS BELOW SIX WEEKS OF
- 8 AGE HAVE NOT BEEN ESTABLISHED. (12) (20) (See DOSAGE AND ADMINISTRATION
- 9 section.)
- In the US, infants receiving two doses of IPV at 2 and 4 months of age, the seroprevalence to all
- three types of poliovirus was demonstrated in 95% to 100% of these infants after two doses of
- 13 vaccine. (12) (13)

15 ADVERSE REACTIONS

- 16 Body System As A Whole
- 17 In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions
- at the site of injection were observed. (3) Erythema, induration and pain occurred in 3.2%, 1%
- and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures of ≥39°C
- 20 (≥102°F) were reported in 38% of vaccinees. Other symptoms included irritability, sleepiness,
- fussiness, and crying. Because IPV was given in a different site but concurrently with Diphtheria
- and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), these systemic reactions could not
- be attributed to a specific vaccine. However, these systemic reactions were comparable in

1 frequency and severity to that reported for DTP given alone without IPV. (12) Although no causal

relationship has been established, deaths have occurred in temporal association after vaccination

3 of infants with IPV. (37)

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5 Four additional US studies using IPOL vaccine in more than 1,300 infants, (12) between 2 to 18

6 months of age administered with DTP at the same time at separate sites or combined have

7 demonstrated that local and systemic reactions were similar when DTP was given alone.

- 1 Table 2 (12): Percentage of Infants Presenting with Local or Systemic Reactions at 6, 24,
- 2 and 48 Hours of Immunization with IPOL Vaccine Administered Intramuscularly
- 3 Concomitantly at Separate Sites with Sanofi[¶] Whole-Cell DTP Vaccine at 2 and 4 Months of
- 4 Age and with Sanofi Acellular Pertussis Vaccine (Tripedia®) at 18 Months of Age

| | AGE AT IMMUNIZATION | | | | | | | | | | |
|----------------------------|---------------------|----------|---------------|--------|-----------|--------------|-------------|-------------|-----------|--|--|
| | | 2 Months | | | 4 Month | ıs | 1 | 8 Months | † | | |
| REACTION | | (n=211) | | | (n=206) | | (n=74) | | | | |
| | 6 Hrs. | 24 Hrs. | 48 Hrs. | 6 Hrs. | 24 Hrs. | 48 Hrs. | 6 Hrs. | 24 Hrs. | 48 Hrs. | | |
| Local, IPOL vaccine alone§ | | | | | | | | | | | |
| Erythema >1" | 0.5% | 0.5% | 0.5% | 1.0% | 0.0% | 0.0% | 1.4% | 0.0% | 0.0% | | |
| Swelling | 11.4% | 5.7% | 0.9% | 11.2% | 4.9% | 1.9% | 2.7% | 0.0% | 0.0% | | |
| Tenderness | 29.4% | 8.5% | 2.8% | 22.8% | 4.4% | 1.0% | 13.5% | 4.1% | 0.0% | | |
| Systemic* | | | | | | | | | | | |
| Fever >102.2°F | 1.0% | 0.5% | 0.5% | 2.0% | 0.5% | 0.0% | 0.0% | 0.0% | 4.2% | | |
| Irritability | 64.5% | 24.6% | 17.5% | 49.5% | 25.7% | 11.7% | 14.7% | 6.7% | 8.0% | | |
| Tiredness | 60.7% | 31.8% | 7.1% | 38.8% | 18.4% | 6.3% | 9.3% | 5.3% | 4.0% | | |
| Anorexia | 16.6% | 8.1% | 4.3% | 6.3% | 4.4% | 2.4% | 2.7% | 1.3% | 2.7% | | |
| Vomiting | 1.9% | 2.8% | 2.8% | 1.9% | 1.5% | 1.0% | 1.3% | 1.3% | 0.0% | | |
| Persistent Crying | | | ants within 7 | | er immuni | zation was 0 | .0% after o | dose one, 1 | .4% after | | |

^{5 ¶} Sanofi Pasteur Inc. formerly known as Aventis Pasteur Inc.

^{6 §} Data are from the IPOL vaccine administration site, given intramuscularly.

^{7 *} The adverse reaction profile includes the concomitant use of Sanofi whole-cell DTP vaccine or Tripedia vaccine

⁸ with IPOL vaccine. Rates are comparable in frequency and severity to that reported for whole-cell DTP given alone.

^{9 †} Children who have been vaccinated with Tripedia vaccine.

1 2 Digestive System 3 Anorexia and vomiting occurred with frequencies not significantly different as reported when 4 DTP was given alone without IPV or OPV. (12) 5 6 Nervous System Although no causal relationship between IPOL vaccine and GBS has been established, (28) GBS 7 8 has been temporally related to administration of another inactivated poliovirus vaccine. 9 10 **Post-marketing Experience** 11 The following adverse events have been identified during postapproval use of IPOL vaccine. 12 Because these events are reported voluntarily from a population of uncertain size, it may not be 13 possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. 14 Adverse events were included based on one or more of the following factors: severity, frequency 15 of reporting or strength of evidence for a causal relationship. 16 **Blood and lymphatic system disorders**: lymphadenopathy 17 General disorders and administration site conditions: agitation, injection site reaction 18 including injection site rash and mass 19 *Immune system disorders*: type I hypersensitivity including allergic reaction, anaphylactic 20 reaction, and anaphylactic shock 21 • Musculoskeletal and connective tissue disorders: arthralgia, myalgia 22 Nervous system disorders: convulsion, febrile convulsion, headache, paresthesia, and 23 somnolence

1 Skin and subcutaneous tissue disorders: rash, urticaria 2 3 **Reporting of Adverse Events** 4 The National Vaccine Injury Compensation Program, established by the National Childhood 5 Vaccine Injury Act of 1986, requires physicians and other healthcare providers who administer 6 vaccines to maintain permanent vaccination records and to report occurrences of certain adverse 7 events to the US Department of Health and Human Services. Reportable events include those 8 listed in the Act for each vaccine and events specified in the package insert as contraindications to 9 further doses of that vaccine. (38) (39) (40) 10 11 Reporting by parents or guardians of all adverse events after vaccine administration should be 12 encouraged. Adverse events following immunization with vaccine should be reported by 13 healthcare providers to the US Department of Health and Human Services (DHHS) Vaccine 14 Adverse Event Reporting System (VAERS). Reporting forms and information about reporting 15 requirements or completion of the form can be obtained from VAERS through a toll-free number 16 1-800-822-7967. (38) (39) (40) 17 18 Healthcare providers also should report these events to the Pharmacovigilance Department, 19 Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

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DOSAGE AND ADMINISTRATION 1 2 Parenteral drug products should be inspected visually for particulate matter and discoloration 3 prior to administration, whenever solution and container permit. The vial and its packaging should 4 be inspected prior to use for evidence of leakage or a faulty seal. If evidence of such defects are 5 observed, the vaccine should not be used. Do not remove the vial stopper or the metal seal holding 6 it in place. 7 8 After preparation of the injection site, using a suitable sterile needle and aseptic technique, 9 immediately administer IPOL vaccine intramuscularly or subcutaneously. In infants and small 10 children, the mid-lateral aspect of the thigh is the preferred site. In older children and adults, IPOL 11 vaccine should be administered intramuscularly or subcutaneously in the deltoid area. IPOL 12 should not be combined through reconstitution or mixed with any other vaccine. 13 14 To help avoid HIV (AIDS), HBV (Hepatitis), and other infectious diseases due to accidental 15 needlesticks, contaminated needles should not be recapped or removed, unless there is no 16 alternative or that such action is required by a specific medical procedure. 17 18 Care should be taken to avoid administering the injection into or near blood vessels and nerves. If 19 blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and 20 repeat procedures using a new dose of vaccine administered at a different site. 21

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

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Children 1 2 The primary series of IPOL vaccine consists of three 0.5 mL doses administered intramuscularly 3 or subcutaneously, preferably eight or more weeks apart and usually at ages 2, 4, and 6 to 18 4 months. Under no circumstances should the vaccine be given more frequently than four weeks 5 apart. The first immunization may be administered as early as six weeks of age. For this series, a 6 booster dose of IPOL vaccine is administered at 4 to 6 years of age. (41) 7 8 **Use with Other Vaccines** 9 From historical data on the antibody responses to diphtheria, tetanus, whole-cell or acellular 10 pertussis, Hib, or hepatitis B vaccines used concomitantly with IPOL vaccine, no interferences 11 have been observed on the immunological end points accepted for clinical protection. (11) (16) 12 (36) (See **DRUG INTERACTIONS** section.) 13 14 If the third dose of IPOL vaccine is given between 12 to 18 months of age, it may be desirable to 15 administer this dose with Measles, Mumps, and Rubella (MMR) vaccine and/or other vaccines 16 using separate syringes at separate sites, (28) but no data on the immunological interference 17 between IPOL vaccine and these vaccines exist. 18

1 **Use in Previously Vaccinated Children** 2 Children and adolescents with a previously incomplete series of polio vaccine should receive 3 sufficient additional doses of IPOL vaccine to complete the series. 4 5 Interruption of the recommended schedule with a delay between doses does not interfere with the 6 final immunity. There is no need to start the series over again, regardless of the time elapsed 7 between doses. 8 9 The need to routinely administer additional doses is unknown at this time. (28) 10 11 Adults 12 **Unvaccinated Adults** 13 A primary series of IPOL vaccine is recommended for unvaccinated adults at increased risk of 14 exposure to poliovirus. While the responses of adults to primary series have not been studied, the 15 recommended schedule for adults is two 0.5 mL doses given at a 1 to 2 month interval and a third 16 0.5 mL dose given 6 to 12 months later. If less than 3 months but more than 2 months are 17 available before protection is needed, three doses of IPOL vaccine should be given at least 1 18 month apart. Likewise, if only 1 or 2 months are available, two 0.5 mL doses of IPOL vaccine 19 should be given at least 1 month apart. If less than 1 month is available, a single 0.5 mL dose of 20 IPOL vaccine is recommended. (28) 21

Incompletely Vaccinated Adults

- 2 Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose
- 3 of OPV, fewer than three doses of conventional IPV or a combination of conventional IPV or
- 4 OPV totaling fewer than three doses should receive at least one 0.5 mL dose of IPOL vaccine.
- 5 Additional doses needed to complete a primary series should be given if time permits. (28)

Completely Vaccinated Adults

- 8 Adults who are at an increased risk of exposure to poliovirus and who have previously completed
- 9 a primary series with one or a combination of polio vaccines can be given a 0.5 mL dose of IPOL
- 10 vaccine.

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12 The preferred injection site of IPOL vaccine for adults is in the deltoid area.

HOW SUPPLIED

15 Vial containing ten 0.5 mL doses: NDC 49281-860-78. Supplied as package: NDC 49281-860-10.

17 **STORAGE**

- 18 The vaccine is stable if stored in the refrigerator at 2°C to 8°C (35°F to 46°F). The vaccine must
- 19 not be frozen.
- 20 Protect from light.

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- 2 FDA Drug Bull 18 (2), 16-18, 1988.
- 3 41 Recommended childhood immunization schedule United States, 1999. MMWR 48: 12-16,
- 4 1999.

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| 1 | Product Information as of . | |
|----|--------------------------------|--------|
| 2 | | |
| 3 | Manufactured by: | |
| 4 | Sanofi Pasteur SA | |
| 5 | Marcy L'Etoile France | |
| 6 | US Govt License #1724 | |
| 7 | | |
| 8 | Distributed by: | |
| 9 | Sanofi Pasteur Inc. | |
| 10 | Swiftwater PA 18370 USA | |
| 11 | 1-800-VACCINE (1-800-822-2463) | |
| 12 | | |
| 13 | | |
| 14 | | |
| 15 | | 969640 |

EXHIBIT 245

Case 2:20-cv-02470-WBS-JDP Document 9

These highlights do not include all the information needed to use PEDIARIX safely and effectively. See full prescribing information for PEDIARIX.

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine], Suspension for Intramuscular Injection Initial U.S. Approval: 2002

----INDICATIONS AND USAGE ----

PEDIARIX is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a 3-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday). (1)

----DOSAGE AND ADMINISTRATION ---

Three doses (0.5-mL each) by intramuscular injection at 2, 4, and 6 months of age. (2.2)

-- DOSAGE FORMS AND STRENGTHS-

Single-dose, prefilled syringes containing a 0.5-mL suspension for injection.

-CONTRAINDICATIONS --

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis-, hepatitis B-, or polioviruscontaining vaccine, or to any component of PEDIARIX. (4.1)
- Encephalopathy within 7 days of administration of a previous pertussiscontaining vaccine. (4.2)
- Progressive neurologic disorders. (4.3)

-- WARNINGS AND PRECAUTIONS ----

- In clinical trials, PEDIARIX was associated with higher rates of fever, relative to separately administered vaccines. (5.1)
- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX

Filed 12/29/20 Page 243 of 497 should be based on potential benefits and risks. (5.2)

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.3)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.4)
- If temperature ≥105°F, collapse or shock-like state, or persistent, inconsolable crying lasting ≥3 hours have occurred within 48 hours after receipt of a pertussis-containing vaccine, or if seizures have occurred within 3 days after receipt of a pertussis-containing vaccine, the decision to give PEDIARIX should be based on potential benefits and risks. (5.5)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with PEDIARIX. (5.6)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.7)

---ADVERSE REACTIONS---

Common solicited adverse reactions following any dose (≥25%) included local injection site reactions (pain, redness, and swelling), fever (≥100.4°F), drowsiness, irritability/fussiness, and loss of appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Glax oS mith Kline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

-- DRUG INTERACTIONS--

Do not mix PEDIARIX with any other vaccine in the same syringe. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/XXXX

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 - 2.2 Recommended Dose and Schedule
 - 2.3 Modified Schedules in Previously Vaccinated Children
 - 2.4 Booster Immunization following PEDIARIX
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
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 - 4.3 Progressive Neurologic Disorder
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PEDIARIX

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^{*}Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

- 3 PEDIARIX is indicated for active immunization against diphtheria, tetanus, pertussis, infection
- 4 caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for
- 5 use as a 3-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers.
- 6 PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th
- 7 birthday).

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8 2 DOSAGE AND ADMINISTRATION

9 2.1 Preparation for Administration

- 10 Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension
- does not occur with vigorous shaking. Parenteral drug products should be inspected visually for
- 12 particulate matter and discoloration prior to administration, whenever solution and container
- permit. If either of these conditions exists, the vaccine should not be administered.
- 14 Attach a sterile needle and administer intramuscularly.
- 15 The preferred administration site is the anterolateral aspect of the thigh for children younger than
- 16 1 year. In older children, the deltoid muscle is usually large enough for an intramuscular
- injection. The vaccine should not be injected in the gluteal area or areas where there may be a
- major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response.
- 19 Do not administer this product intravenously, intradermally, or subcutaneously.

20 2.2 Recommended Dose and Schedule

- 21 Immunization with PEDIARIX consists of 3 doses of 0.5 mL each by intramuscular injection at
- 22 2, 4, and 6 months of age (at intervals of 6 to 8 weeks, preferably 8 weeks). The first dose may
- be given as early as 6 weeks of age. Three doses of PEDIARIX constitute a primary
- 24 immunization course for diphtheria, tetanus, pertussis, and poliomyelitis and the complete
- vaccination course for hepatitis B.

26 2.3 Modified Schedules in Previously Vaccinated Children

- 27 Children Previously Vaccinated with Diphtheria and Tetanus Toxoids and Acellular Pertussis
- 28 Vaccine Adsorbed (DTaP)
- 29 PEDIARIX may be used to complete the first 3 doses of the DTaP series in children who have
- 30 received 1 or 2 doses of INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis
- 31 Vaccine Adsorbed), manufactured by GlaxoSmithKline, identical to the DTaP component of
- 32 PEDIARIX [see Description (11)] and are also scheduled to receive the other vaccine
- components of PEDIARIX. Data are not available on the safety and effectiveness of using
- 34 PEDIARIX following 1 or more doses of a DTaP vaccine from a different manufacturer.

35 Children Previously Vaccinated with Hepatitis B Vaccine

- 36 PEDIARIX may be used to complete the hepatitis B vaccination series following 1 or 2 doses of
- another hepatitis B vaccine (monovalent or as part of a combination vaccine), including vaccines
- from other manufacturers, in children born of HBsAg-negative mothers who are also scheduled
- 39 to receive the other vaccine components of PEDIARIX.
- 40 A 3-dose series of PEDIARIX may be administered to infants born of HBsAg-negative mothers
- and who received a dose of hepatitis B vaccine at or shortly after birth. However, data are limited
- regarding the safety of PEDIARIX in such infants [see Adverse Reactions (6.1)]. There are no
- data to support the use of a 3-dose series of PEDIARIX in infants who have previously received
- 44 more than 1 dose of hepatitis B vaccine.
- 45 <u>Children Previously Vaccinated with Inactivated Poliovirus Vaccine (IPV)</u>
- 46 PEDIARIX may be used to complete the first 3 doses of the IPV series in children who have
- 47 received 1 or 2 doses of IPV from a different manufacturer and are also scheduled to receive the
- 48 other vaccine components of PEDIARIX.

49 2.4 Booster Immunization following PEDIARIX

- 50 Children who have received a 3-dose series with PEDIARIX should complete the DTaP and IPV
- series according to the recommended schedule. Because the pertussis antigens contained in
- 52 INFANRIX and KINRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed
- and Inactivated Poliovirus Vaccine), manufactured by GlaxoSmithKline, are the same as those in
- 54 PEDIARIX, these children should receive INFANRIX as their fourth dose of DTaP and either
- 55 INFANRIX or KINRIX as their fifth dose of DTaP, according to the respective prescribing
- information for these vaccines. KINRIX or another manufacturer's IPV may be used to complete
- 57 the 4-dose IPV series according to the respective prescribing information.

58 3 DOSAGE FORMS AND STRENGTHS

- 59 PEDIARIX is a suspension for injection available in 0.5-mL single-dose prefilled TIP-LOK
- 60 syringes.

61 4 CONTRAINDICATIONS

62 4.1 Hypersensitivity

- 63 A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-,
- 64 tetanus toxoid-, pertussis antigen-, hepatitis B-, or poliovirus-containing vaccine or any
- component of this vaccine, including yeast, neomycin, and polymyxin B, is a contraindication to
- administration of PEDIARIX [see Description (11)].

67 4.2 Encephalopathy

68 Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days

- of administration of a previous dose of a pertussis-containing vaccine that is not attributable to
- another identifiable cause is a contraindication to administration of any pertussis-containing
- 71 vaccine, including PEDIARIX.

72 4.3 Progressive Neurologic Disorder

- 73 Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or
- 74 progressive encephalopathy, is a contraindication to administration of any pertussis-containing
- vaccine, including PEDIARIX. PEDIARIX should not be administered to individuals with such
- 76 conditions until the neurologic status is clarified and stabilized.

77 5 WARNINGS AND PRECAUTIONS

78 **5.1** Fever

- 79 In clinical trials, administration of PEDIARIX in infants was associated with higher rates of
- 80 fever relative to separately administered vaccines [see Adverse Reactions (6.1)].

81 5.2 Guillain-Barré Syndrome

- 82 If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus
- 83 toxoid, the decision to give PEDIARIX or any vaccine containing tetanus toxoid should be based
- on careful consideration of the potential benefits and possible risks.

85 **5.3** Latex

- 86 The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic
- 87 reactions.

88 **5.4** Syncope

- 89 Syncope (fainting) can occur in association with administration of injectable vaccines, including
- 90 PEDIARIX. Syncope can be accompanied by transient neurological signs such as visual
- 91 disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to
- avoid falling injury and to restore cerebral perfusion following syncope.

93 5.5 Adverse Reactions following Prior Pertussis Vaccination

- 94 If any of the following reactions occur in temporal relation to receipt of a vaccine containing a
- 95 pertussis component, the decision to give any pertussis-containing vaccine, including
- 96 PEDIARIX, should be based on careful consideration of the potential benefits and possible risks:
- Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

101 5.6 Children at Risk for Seizures

For children at higher risk for seizures than the general population, an appropriate antipyretic

- may be administered at the time of vaccination with a vaccine containing a pertussis component,
- including PEDIARIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination
- 105 fever.

106 5.7 Apnea in Premature Infants

- Apnea following intramuscular vaccination has been observed in some infants born prematurely.
- Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants
- born prematurely should be based on consideration of the individual infant's medical status and
- the potential benefits and possible risks of vaccination.

111 5.8 Preventing and Managing Allergic Vaccine Reactions

- Prior to administration, the healthcare provider should review the immunization history for
- possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an
- assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of
- immediate allergic reactions must be immediately available should an acute anaphylactic
- 116 reaction occur.

117 6 ADVERSE REACTIONS

118 6.1 Clinical Trials Experience

- Because clinical trials are conducted under widely varying conditions, adverse reaction rates
- observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical
- trials of another vaccine and may not reflect the rates observed in practice.
- 122 A total of 23,849 doses of PEDIARIX have been administered to 8,088 infants who received 1 or
- more doses as part of the 3-dose series during 14 clinical studies. Common adverse reactions that
- occurred in ≥25% of subjects following any dose of PEDIARIX included local injection site
- reactions (pain, redness, and swelling), fever, drowsiness, irritability/fussiness, and loss of
- appetite. In comparative studies (including the German and U.S. studies described below),
- administration of PEDIARIX was associated with higher rates of fever relative to separately
- administered vaccines [see Warnings and Precautions (5.1)]. The prevalence of fever was
- highest on the day of vaccination and the day following vaccination. More than 96% of episodes
- of fever resolved within the 4-day period following vaccination (i.e., the period including the day
- of vaccination and the next 3 days).
- In the largest of the 14 studies conducted in Germany, safety data were available for 4,666
- infants who received PEDIARIX administered concomitantly at separate sites with 1 of 4
- 134 Haemophilus influenzae type b (Hib) conjugate vaccines (GlaxoSmithK line [licensed in the
- United States only for booster immunization], Wyeth Pharmaceuticals Inc. [no longer licensed in
- the United States], Sanofi Pasteur SA [U.S.-licensed], or Merck & Co, Inc. [U.S.-licensed]) at 3,
- 4, and 5 months of age and for 768 infants in the control group that received separate U.S.-
- licensed vaccines (INFANRIX, Hib conjugate vaccine [Sanofi Pasteur SA], and oral poliovirus

- vaccine [OPV] [Wyeth Pharmaceuticals, Inc.; no longer licensed in the United States]). In this
- study, information on adverse events that occurred within 30 days following vaccination was
- 141 collected. More than 95% of study participants were white.
- In a U.S. study, the safety of PEDIARIX administered to 673 infants was compared with the
- safety of separately administered INFANRIX, ENGERIX-B [Hepatitis B Vaccine
- (Recombinant)], and IPV (Sanofi Pasteur SA) in 335 infants. In both groups, infants received
- 145 Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the United States) and
- 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at
- separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited
- local reactions and general adverse reactions were collected by parents using standardized diary
- cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next
- 150 3 days). Telephone follow-up was conducted 1 month and 6 months after the third vaccination to
- inquire about serious adverse events. At the 6-month follow-up, information also was collected
- on new onset of chronic illnesses. A total of 638 subjects who received PEDIARIX and 313
- subjects who received INFANRIX, ENGERIX-B, and IPV completed the 6-month follow-up.
- Among subjects in both study groups combined, 69% were white, 18% were Hispanic, 7% were
- black, 3% were Oriental, and 3% were of other racial/ethnic groups.
- 156 <u>Solicited Adverse Reactions</u>
- Data on solicited local reactions and general adverse reactions from the U.S. safety study are
- presented in Table 1. This study was powered to evaluate fever >101.3°F following Dose 1. The
- rate of fever ≥100.4°F following each dose was significantly higher in the group that received
- 160 PEDIARIX compared with separately administered vaccines. Other statistically significant
- differences between groups in rates of fever, as well as other solicited adverse reactions, are
- noted in Table 1. Medical attention (a visit to or from medical personnel) for fever within 4 days
- following vaccination was sought in the group who received PEDIARIX for 8 infants after the
- first dose (1.2%), 1 infant following the second dose (0.2%), and 5 infants following the third
- dose (0.8%) (Table 1). Following Dose 2, medical attention for fever was sought for 2 infants
- 166 (0.6%) who received separately administered vaccines (Table 1). Among infants who had a
- medical visit for fever within 4 days following vaccination, 9 of 14 who received PEDIARIX
- and 1 of 2 who received separately administered vaccines, had 1 or more diagnostic studies
- performed to evaluate the cause of fever.

- 170 Table 1. Percentage of Infants with Solicited Local and General Adverse Reactions within
- 4 Days of Vaccination^a at 2, 4, and 6 Months of Age with PEDIARIX Administered
- 172 Concomitantly with Hib Conjugate Vaccine and 7-Valent Pneumococcal Conjugate
- 173 Vaccine (PCV7) or with Separate Concomitant Administration of INFANRIX,
- 174 ENGERIX-B, IPV, Hib Conjugate Vaccine, and PCV7 (Modified Intent-to-Treat Cohort)

| ENGERIA-D, II V, IIIb Conjugate | | RIX, Hib | | INFANRIX, ENGERIX-B, | | | |
|------------------------------------|----------------|-----------------|-----------------|--------------------------|--------|--------|--|
| | | & PCV7 | ŕ | IPV, Hib Vaccine, & PCV7 | | | |
| Adverse Reaction | Dose 1 | Dose 2 | Dose 3 | Dose 1 | Dose 2 | Dose 3 | |
| Local ^b | | | | | | | |
| n | 671 | 653 | 648 | 335 | 323 | 315 | |
| Pain, any | 36 | 36 | 31 | 32 | 30 | 30 | |
| Pain, Grade 2 or 3 | 12 | 11 | 11 | 9 | 9 | 9 | |
| Pain, Grade 3 | 2 | 3 | 2 | 3 | 2 | 1 | |
| Redness, any | 25° | 37 | 40 | 18 | 33 | 39 | |
| Redness, >5 mm | 6 ^c | 10 ^c | 13 ^c | 2 | 6 | 7 | |
| Redness, >20 mm | 1 | 1° | 3 | 0 | 0 | 2 | |
| Swelling, any | 17° | 27° | 29 | 10 | 20 | 25 | |
| Swelling, >5 mm | 6c | 10 ^c | 9c | 2 | 5 | 4 | |
| Swelling, >20 mm | 2 | 3° | 3 | 1 | 0 | 1 | |
| General | | | | | | | |
| n | 667 | 644 | 645 | 333 | 321 | 311 | |
| Fever ^d , ≥100.4°F | 28c | 39c | 34 ^c | 20 | 30 | 24 | |
| Fever ^d , >101.3°F | 7 | 14 ^c | 9 | 5 | 10 | 6 | |
| Fever ^d , >102.2°F | 2 ^c | 4 | 3 | 0 | 3 | 2 | |
| Fever ^d , >103.1°F | 1 | 1 | 1 | 0 | 0 | 0 | |
| Fever ^d , M.A. | 1c | 0 | 1 | 0 | 1 | 0 | |
| n | 671 | 653 | 648 | 335 | 323 | 315 | |
| Drowsiness, any | 57 | 52 | 41 | 54 | 48 | 38 | |
| Drowsiness, Grade 2 or 3 | 16 | 14 | 11 | 18 | 12 | 11 | |
| Drowsiness, Grade 3 | 3 | 1 | 1 | 4 | 1 | 2 | |
| Irritability/Fussiness, any | 61 | 65 | 61 | 62 | 62 | 57 | |
| Irritability/Fussiness, Grade 2 or | 20 | 28° | 25° | 19 | 21 | 19 | |
| 3 | | | | | | | |
| Irritability/Fussiness, Grade 3 | 3 | 4 | 4 | 4 | 3 | 3 | |
| Loss of appetite, any | 30 | 31 | 26 | 28 | 27 | 24 | |
| Loss of appetite, Grade 2 or 3 | 7 | 8c | 6 | 5 | 3 | 5 | |
| Loss of appetite, Grade 3 | 1 | 0 | 0 | 1 | 0 | 0 | |

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the United States);

¹⁷⁶ PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

¹⁷⁷ Modified intent-to-treat cohort = All vaccinated subjects for whom safety data were available.

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- n = Number of infants for whom at least 1 symptom sheet was completed; for fever, numbers
- exclude missing temperature recordings or tympanic measurements.
- 180 M.A. = Medically attended (a visit to or from medical personnel).
- 181 Grade 2 defined as sufficiently discomforting to interfere with daily activities.
- 182 Grade 3 defined as preventing normal daily activities.
- a Within 4 days of vaccination defined as day of vaccination and the next 3 days.
- b Local reactions at the injection site for PEDIARIX or INFANRIX.
- 185 c Rate significantly higher in the group that received PEDIARIX compared with separately
- administered vaccines (P value <0.05 [2-sided Fisher Exact test] or the 95% CI on the
- difference between groups [Separate minus PEDIARIX] does not include 0).
- d Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive
- 189 equivalent rectal temperature.

190 Serious Adverse Events

- 191 Within 30 days following any dose of vaccine in the U.S. safety study in which all subjects
- received concomitant Hib and pneumococcal conjugate vaccines, 7 serious adverse events were
- reported in 7 subjects (1% [7/673]) who received PEDIARIX (1 case each of pyrexia,
- 194 gastroenteritis, and culture-negative clinical sepsis and 4 cases of bronchiolitis) and 5 serious
- adverse events were reported in 4 subjects (1% [4/335]) who received INFANRIX, ENGERIX-
- B, and IPV (uteropelvic junction obstruction and testicular atrophy in 1 subject and 3 cases of
- 197 bronchiolitis).
- 198 Deaths
- In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of PEDIARIX and 1
- death was reported among 2,287 (0.04%) recipients of comparator vaccines. Causes of death in
- the group that received PEDIARIX included 2 cases of Sudden Infant Death Syndrome (SIDS)
- and 1 case of each of the following: convulsive disorder, congenital immunodeficiency with
- sepsis, and neuroblastoma. One case of SIDS was reported in the comparator group. The rate of
- SIDS among all recipients of PEDIARIX across the 14 trials was 0.25/1,000. The rate of SIDS
- observed for recipients of PEDIARIX in the German safety study was 0.2/1,000 infants (reported
- rate of SIDS in Germany in the latter part of the 1990s was 0.7/1,000 newborns). The reported
- rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births. By chance alone,
- some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.
- 209 Onset of Chronic Illnesses
- In the U.S. safety study in which all subjects received concomitant Hib and pneumococcal
- conjugate vaccines, 21 subjects (3%) who received PEDIARIX and 14 subjects (4%) who
- 212 received INFANRIX, ENGERIX-B, and IPV reported new onset of a chronic illness during the
- 213 period from 1 to 6 months following the last dose of study vaccines. Among the chronic illnesses
- 214 reported in the subjects who received PEDIARIX, there were 4 cases of asthma and 1 case each

- of diabetes mellitus and chronic neutropenia. There were 4 cases of asthma in subjects who
- 216 received INFANRIX, ENGERIX-B, and IPV.
- 217 <u>Seizures</u>
- In the German safety study over the entire study period, 6 subjects in the group that received
- PEDIARIX (n = 4,666) reported seizures. Two of these subjects had a febrile seizure, 1 of whom
- also developed afebrile seizures. The remaining 4 subjects had afebrile seizures, including 2 with
- infantile spasms. Two subjects reported seizures within 7 days following vaccination (1 subject
- 222 had both febrile and afebrile seizures, and 1 subject had afebrile seizures), corresponding to a
- rate of 0.22 seizures per 1,000 doses (febrile seizures 0.07 per 1,000 doses, afebrile seizures 0.14
- per 1,000 doses). No subject who received concomitant INFANRIX, Hib vaccine, and OPV
- 225 (n = 768) reported seizures. In a separate German study that evaluated the safety of INFANRIX
- 226 in 22,505 infants who received 66,867 doses of INFANRIX administered as a 3-dose primary
- series, the rate of seizures within 7 days of vaccination with INFANRIX was 0.13 per 1,000
- doses (febrile seizures 0.0 per 1,000 doses, afebrile seizures 0.13 per 1,000 doses).
- Over the entire study period in the U.S. safety study in which all subjects received concomitant
- 230 Hib and pneumococcal conjugate vaccines, 4 subjects in the group that received PEDIARIX
- (n = 673) reported seizures. Three of these subjects had a febrile seizure and 1 had an afebrile
- seizure. Over the entire study period, 2 subjects in the group that received INFANRIX,
- ENGERIX-B, and IPV (n = 335) reported febrile seizures. There were no afebrile seizures in this
- group. No subject in either study group had seizures within 7 days following vaccination.
- 235 Other Neurological Events of Interest
- No cases of hypotonic-hyporesponsiveness or encephalopathy were reported in either the
- German or U.S. safety studies.
- 238 Safety of PEDIARIX after a Previous Dose of Hepatitis B Vaccine
- 239 Limited data are available on the safety of administering PEDIARIX after a previous dose of
- 240 hepatitis B vaccine. In 2 separate studies, 160 Moldovan infants and 96 U.S. infants,
- respectively, received 3 doses of PEDIARIX following 1 previous dose of hepatitis B vaccine.
- Neither study was designed to detect significant differences in rates of adverse events associated
- 243 with PEDIARIX administered after a previous dose of hepatitis B vaccine compared with
- 244 PEDIARIX administered without a previous dose of hepatitis B vaccine.

245 6.2 Postmarketing Safety Surveillance Study

- In a safety surveillance study conducted at a health maintenance organization in the United
- 247 States, infants who received 1 or more doses of PEDIARIX from approximately mid-2003
- 248 through mid-2005 were compared with age-, gender-, and area-matched historical controls who
- received 1 or more doses of separately administered U.S.-licensed DTaP vaccine from 2002
- 250 through approximately mid-2003. Only infants who received 7-valent pneumococcal conjugate
- vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with PEDIARIX or DTaP vaccine were

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| 252 | included in the cohorts. Other U.Slicensed vaccines were administered according to routine |
|-----|---|
| 253 | practices at the study sites, but concomitant administration with PEDIARIX or DTaP was not a |
| 254 | criterion for inclusion in the cohorts. A birth dose of hepatitis B vaccine had been administered |
| 255 | routinely to infants in the historical DTaP control cohort, but not to infants who received |
| 256 | PEDIARIX. For each of Doses 1-3, a random sample of 40,000 infants who received PEDIARIX |
| 257 | was compared with the historical DTaP control cohort for the incidence of seizures (with or |
| 258 | without fever) during the 8-day period following vaccination. For each dose, random samples of |
| 259 | 7,500 infants in each cohort were also compared for the incidence of medically-attended fever |
| 260 | (fever ≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient |
| 261 | visit) during the 4-day period following vaccination. Possible seizures and medical visits |
| 262 | plausibly related to fever were identified by searching automated inpatient and outpatient data |
| 263 | files. Medical record reviews of identified events were conducted to verify the occurrence of |
| 264 | seizures or medically-attended fever. The incidence of verified seizures and medically-attended |
| 265 | fever from this study are presented in Table 2. |

Table 2. Percentage of Infants with Seizures (with or without Fever) within 8 Days of

Vaccination and Medically-Attended Fever within 4 Days of Vaccination with PEDIARIX

268 Compared with Historical Controls

267

276

| Compared with This | PEDIARIX | | | Historical DTaP Controls | | | Difference (PEDIARIX–DTaP Controls) |
|--|----------|----|---------------|--------------------------|----|---------------|---|
| Adverse Reaction | N | n | % (95% CI) | N | n | % (95% CI) | % (95% CI) |
| All Seizures (with or without fever) | | | | | | | |
| Dose 1, Days 0-7 | 40,000 | 7 | 0.02 | 39,232 | 6 | 0.02 | 0.00 |
| | | | (0.01, 0.04) | | | (0.01, 0.03) | (-0.02, 0.02) |
| Dose 2, Days 0-7 | 40,000 | 3 | 0.01 | 37,405 | 4 | 0.01 | 0.00 |
| | | | (0.00, 0.02) | | | (0.00, 0.03) | (-0.02, 0.01) |
| Dose 3, Days 0-7 | 40,000 | 6 | 0.02 | 40,000 | 5 | 0.01 | 0.00 |
| | | | (0.01, 0.03) | | | (0.00, 0.03) | (-0.01, 0.02) |
| Totaldoses | 120,000 | 16 | 0.01 | 116,637 | 15 | 0.01 | 0.00 |
| | | | (0.01, 0.02) | | | (0.01, 0.02) | (-0.01, 0.01) |
| Medically-Attended Fever ^a | | | | | | | |
| Dose 1, Days 0-3 | 7,500 | 14 | 0.19 | 7,500 | 14 | 0.19 | 0.00 |
| | | | (0.11, 0.30) | | | (0.11, 0.30) | (-0.14, 0.14) |
| Dose 2, Days 0-3 | 7,500 | 25 | 0.33 | 7,500 | 15 | 0.20 | 0.13 |
| | | | (0.22, 0.48) | | | (0.11, 0.33) | (-0.03, 0.30) |
| Dose 3, Days 0-3 | 7,500 | 21 | 0.28 | 7,500 | 19 | 0.25 | 0.03 |
| | | | (0.17, 0.43) | | | (0.15, 0.39) | (-0.14, 0.19) |
| Totaldoses | 22,500 | 60 | 0.27 | 22,500 | 48 | 0.21 | 0.05 |
| | | | (0.20, 0.34) | | | (0.16, 0.28) | (-0.01, 0.14) |

- 269 DTaP any U.S.-licensed DTaP vaccine. Infants received 7-valent pneumococcal conjugate
- vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with each dose of PEDIARIX or DTaP.
- Other U.S.-licensed vaccines were administered according to routine practices at the study sites.
- N = Number of subjects in the given cohort.
- n = Number of subjects with reactions reported in the given cohort.
- ^a Medically-attended fever defined as fever ≥100.4°F that resulted in hospitalization, an
- emergency department visit, or an outpatient visit.

6.3 Postmarketing Spontaneous Reports for PEDIARIX

- In addition to reports in clinical trials for PEDIARIX, the following adverse reactions have been
- 278 identified during postapproval use of PEDIARIX. Because these reactions are reported
- voluntarily from a population of uncertain size, it is not always possible to reliably estimate their
- 280 frequency or establish a causal relationship to vaccine exposure.

281 Cardiac Disorders 282 Cyanosis. 283 Gastrointestinal Disorders Diarrhea, vomiting. 284 285 General Disorders and Administration Site Conditions 286 Fatigue, injection site cellulitis, injection site induration, injection site itching, injection site 287 nodule/lump, injection site reaction, injection site vesicles, injection site warmth, limb pain, limb swelling. 288 289 Immune System Disorders 290 Anaphylactic reaction, anaphylactoid reaction, hypersensitivity. 291 Infections and Infestations 292 Upper respiratory tract infection. 293 **Investigations** 294 Abnormal liver function tests. 295 Nervous System Disorders 296 Bulging fontanelle, depressed level of consciousness, encephalitis, hypotonia, hypotonic-297 hyporesponsive episode, lethargy, somnolence, syncope. 298 Psychiatric Disorders 299 Crying, insomnia, nervousness, restlessness, screaming, unusual crying. 300 Respiratory, Thoracic, and Mediastinal Disorders 301 Apnea, cough, dyspnea. 302 Skin and Subcutaneous Tissue Disorders 303 Angioedema, erythema, rash, urticaria. 304 Vascular Disorders 305 Pallor, petechiae. 306 6.4 Postmarketing Spontaneous Reports for INFANRIX and/or ENGERIX-B 307 The following adverse reactions have been identified during postapproval use of INFANRIX 308 and/or ENGERIX-B in children younger than 7 years but not already reported for PEDIARIX. 309 Because these reactions are reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to vaccine

310

311

exposure.

- 312 <u>Blood and Lymphatic System Disorders</u>
- 313 Idiopathic thrombocytopenic purpura, a,b lymphadenopathy, a thrombocytopenia. a,b
- 314 Gastrointestinal Disorders
- 315 Abdominal pain, b intussusception, a,b nausea.b
- 316 General Disorders and Administration Site Conditions
- 317 Asthenia, b malaise. b
- 318 Hepatobiliary Disorders
- 319 Jaundice.b
- 320 Immune System Disorders
- 321 Anaphylactic shock, a serum sickness–like disease. b
- 322 Musculoskeletal and Connective Tissue Disorders
- 323 Arthralgia, b arthritis, b muscular weakness, b myalgia. b
- 324 Nervous System Disorders
- Encephalopathy, headache, meningitis, neuritis, neuropathy, paralysis.
- 326 Skin and Subcutaneous Tissue Disorders
- 327 Alopecia, b erythema multiforme, b lichen planus, b pruritus, a, b Stevens Johnson syndrome. a
- 328 Vascular Disorders
- 329 Vasculitis.b
- ^a Following INFANRIX (licensed in the United States in 1997).
- b Following ENGERIX-B (licensed in the United States in 1989).
- 332 7 DRUG INTERACTIONS
- 333 7.1 Concomitant Vaccine Administration
- 334 Immune responses following concomitant administration of PEDIARIX, Hib conjugate vaccine
- 335 (Wyeth Pharmaceuticals Inc.; no longer licensed in the U.S.), and 7-valent pneumococcal
- conjugate vaccine (Wyeth Pharmaceuticals Inc.) were evaluated in a clinical trial *[see Clinical]*
- 337 Studies (14.3)].
- When PEDIARIX is administered concomitantly with other injectable vaccines, they should be
- 339 given with separate syringes and at different injection sites. PEDIARIX should not be mixed
- with any other vaccine in the same syringe.

341 7.2 Immunos uppressive Therapies

- 342 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
- drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune
- response to PEDIARIX.

345 8 USE IN SPECIFIC POPULATIONS

346 **8.4** Pediatric Use

- 347 Safety and effectiveness of PEDIARIX were established in the age group 6 weeks through
- 6 months on the basis of clinical studies [see Adverse Reactions (6.1), Clinical Studies (14.1,
- 349 14.2). Safety and effectiveness of PEDIARIX in the age group 7 months through 6 years are
- supported by evidence in infants aged 6 weeks through 6 months. Safety and effectiveness of
- 351 PEDIARIX in infants younger than 6 weeks and children aged 7 to 16 years have not been
- 352 evaluated.

353 11 **DESCRIPTION**

- 354 PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B
- 355 (Recombinant) and Inactivated Poliovirus Vaccine] is a noninfectious, sterile vaccine for
- intramuscular administration. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria
- toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis toxin (PT), 25 mcg of
- filamentous hemagglutinin (FHA), 8 mcg of pertactin (69 kiloDalton outer membrane protein),
- 359 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2
- poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The diphtheria, tetanus, and
- pertussis components are the same as those in INFANRIX and KINRIX. The hepatitis B surface
- antigen is the same as that in ENGERIX-B.
- 363 The diphtheria toxin is produced by growing Corynebacterium diphtheriae (C. diphtheriae) in
- Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium*
- 365 tetani (C. tetani) in a modified Latham medium derived from bovine casein. The bovine
- materials used in these extracts are sourced from countries which the United States Department
- of Agriculture (USDA) has determined neither have nor present an undue risk for bovine
- 368 spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated
- by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.
- The acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis*
- 371 (B. pertussis) culture grown in modified Stainer-Scholte liquid medium. PT and FHA are
- isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and
- 373 flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT
- is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with
- 375 formaldehyde.
- 376 The hepatitis B surface antigen is obtained by culturing genetically engineered Saccharomyces

- 377 cerevisiae (S. cerevisiae) cells, which carry the surface antigen gene of the hepatitis B virus, in
- 378 synthetic medium. The surface antigen expressed in the S. cerevisiae cells is purified by several
- 379 physiochemical steps, which include precipitation, ion exchange chromatography, and
- 380 ultrafiltration.
- 381 The inactivated poliovirus component is an enhanced potency component. Each of the 3 strains
- of poliovirus is individually grown in VERO cells, a continuous line of monkey kidney cells,
- cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during VERO cell
- 384 culture and/or virus culture. Calf serum is sourced from countries the USDA has determined
- neither have nor present an undue risk for BSE. After clarification, each viral suspension is
- purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated
- with formaldehyde. The 3 purified viral strains are then pooled to form a trivalent concentrate.
- Diphtheria and tetanus toxoids and pertussis antigens (inactivated PT, FHA, and pertactin) are
- 389 individually adsorbed onto aluminum hydroxide. The hepatitis B component is adsorbed onto
- 390 aluminum phosphate.
- 391 Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing
- antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis component
- 393 (inactivated PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay
- 394 (ELISA) on sera from previously immunized mice. Potency of the hepatitis B component is
- established by HBsAg ELISA. The potency of the inactivated poliovirus component is
- determined by using the D-antigen ELISA and by a poliovirus-neutralizing cell culture assay on
- sera from previously immunized rats.
- Each 0.5-mL dose contains aluminum salts as adjuvant (not more than 0.85 mg aluminum by
- assay) and 4.5 mg of sodium chloride. Each dose also contains ≤100 mcg of residual
- 400 formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80). Neomycin sulfate and polymyxin B
- are used in the poliovirus vaccine manufacturing process and may be present in the final vaccine
- at ≤ 0.05 ng neomycin and ≤ 0.01 ng polymyxin B per dose. The procedures used to manufacture
- 403 the HBsAg antigen result in a product that contains ≤5% yeast protein.
- The tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with
- 405 natural rubber latex.
- 406 PEDIARIX is formulated without preservatives.

407 12 CLINICAL PHARMACOLOGY

- 408 12.1 Mechanism of Action
- 409 Diphtheria
- Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of C.
- 411 diphtheriae. Protection against disease is due to the development of neutralizing antibodies to the
- 412 diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving

- some degree of protection; a level of 0.1 IU/mL is regarded as protective.²
- 414 Tetanus
- Tetanus is an acute toxin-mediated disease caused by a potent exotoxin released by *C. tetani*.
- Protection against disease is due to the development of neutralizing antibodies to the tetanus
- 417 toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays,
- 418 is considered the minimum protective level.^{3,4} A level ≥0.1 IU/mL is considered protective.⁵
- 419 Pertussis
- 420 Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role
- of the different components produced by *B. pertussis* in either the pathogenesis of, or the
- 422 immunity to, pertussis is not well understood. There is no established serological correlate of
- 423 protection for pertussis.
- 424 Hepatitis B
- Infection with hepatitis B virus can have serious consequences including acute massive hepatic
- 426 necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for
- 427 cirrhosis and hepatocellular carcinoma.
- 428 Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection
- 429 against hepatitis B virus infection.⁶
- 430 Poliomyelitis
- Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus
- have been identified (Types 1, 2, and 3). Poliovirus-neutralizing antibodies confer protection
- 433 against poliomyelitis disease.⁷
- 434 13 NONCLINICAL TOXICOLOGY
- 435 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- PEDIARIX has not been evaluated for carcinogenic or mutagenic potential or for impairment of
- 437 fertility.
- 438 14 CLINICAL STUDIES
- The efficacy of PEDIARIX is based on the immunogenicity of the individual antigens compared
- with licensed vaccines. Serological correlates of protection exist for the diphtheria, tetanus,
- hepatitis B, and poliovirus components. The efficacy of the pertussis component, which does not
- have a well-established correlate of protection, was determined in clinical trials of INFANRIX.
- 443 14.1 Efficacy of INFANRIX
- Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.
- 445 A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial

- conducted in Italy, sponsored by the National Institutes of Health (NIH), assessed the absolute
- protective efficacy of INFANRIX when administered at 2, 4, and 6 months of age. The
- 448 population used in the primary analysis of the efficacy of INFANRIX included 4,481 infants
- 449 vaccinated with INFANRIX and 1.470 DT vaccinees. After 3 doses, the absolute protective
- 450 efficacy of INFANRIX against WHO-defined typical pertussis (21 days or more of paroxysmal
- cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76%,
- 452 89%). When the definition of pertussis was expanded to include clinically milder disease, with
- infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was 71%
- 454 (95% CI: 60%, 78%) against >7 days of any cough and 73% (95% CI: 63%, 80%) against
- 455 ≥14 days of any cough. A longer unblinded follow-up period showed that after 3 doses and with
- 456 no booster dose in the second year of life, the efficacy of INFANRIX against WHO-defined
- 457 pertussis was 86% (95% CI: 79%, 91%) among children followed to 6 years of age. For details
- see INFANRIX prescribing information.
- 459 A prospective efficacy trial was also conducted in Germany employing a household contact
- study design. In this study, the protective efficacy of INFANRIX administered to infants at 3, 4,
- and 5 months of age against WHO-defined pertussis was 89% (95% CI: 77%, 95%). When the
- definition of pertussis was expanded to include clinically milder disease, with infection
- 463 confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any
- 464 cough was 67% (95% CI: 52%, 78%) and against ≥7 days of paroxysmal cough was 81% (95%
- 465 CI: 68%, 89%). For details see INFANRIX prescribing information.

466 14.2 Immunological Evaluation of PEDIARIX

- In a U.S. multicenter study, infants were randomized to 1 of 3 groups: (1) a combination vaccine
- group that received PEDIARIX concomitantly with Hib conjugate vaccine (Wyeth
- Pharmaceuticals Inc.; no longer licensed in the United States) and U.S.-licensed 7-valent
- pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.); (2) a separate vaccine group that
- 471 received U.S.-licensed INFANRIX, ENGERIX-B, and IPV (Sanofi Pasteur SA) concomitantly
- with the same Hib and pneumococcal conjugate vaccines; and (3) a staggered vaccine group that
- 473 received PEDIARIX concomitantly with the same Hib conjugate vaccine but with the same
- 474 pneumococcal conjugate vaccine administered 2 weeks later. The schedule of administration was
- 2, 4, and 6 months of age. Infants either did not receive a dose of hepatitis B vaccine prior to
- 476 enrollment or were permitted to receive 1 dose of hepatitis B vaccine administered at least
- 477 30 days prior to enrollment. For the separate vaccine group, ENGERIX-B was not administered
- at 4 months of age to subjects who received a dose of hepatitis B vaccine prior to enrollment.
- Among subjects in all 3 vaccine groups combined, 84% were white, 7% were Hispanic, 6% were
- black, 0.7% were Oriental, and 2.4% were of other racial/ethnic groups.
- The immune responses to the pertussis (PT, FHA, and pertactin), diphtheria, tetanus, poliovirus,
- and hepatitis B antigens were evaluated in sera obtained 1 month (range: 20 to 60 days) after the
- 483 third dose of PEDIARIX or INFANRIX. Geometric mean antibody concentrations (GMCs)
- adjusted for pre-vaccination values for PT, FHA, and pertactin and the seroprotection rates for

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| 185 | diphtheria, tetanus, and the polioviruses among subjects who received PEDIARIX in the |
|-----|--|
| 186 | combination vaccine group were shown to be non-inferior to those achieved following separately |
| 187 | administered vaccines (Table 3). |
| 188 | Because of differences in the hepatitis B vaccination schedule among subjects in the study, no |
| 189 | clinical limit for non-inferiority was pre-defined for the hepatitis B immune response. However, |
| 190 | in a previous U.S. study, non-inferiority of PEDIARIX relative to separately administered |
| 191 | INFANRIX, ENGERIX-B, and an oral poliovirus vaccine, with respect to the hepatitis B |
| 192 | immune response was demonstrated. |

- Table 3. Antibody Responses following PEDIARIX as Compared with Separate
- 494 Concomitant Administration of INFANRIX, ENGERIX-B, and IPV (1 Month^a after
- 495 Administration of Dose 3) in Infants Vaccinated at 2, 4, and 6 Months of Age when
- 496 Administered Concomitantly with Hib Conjugate Vaccine and Pneumococcal Conjugate

497 Vaccine (PCV7)

| vaccine (1 C v /) | PEDIARIX, Hib Vaccine, & PCV7 | INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7 |
|---------------------------|----------------------------------|--|
| Antibody | (n = 154-168) | (n = 141-155) |
| Anti-diphtheria Toxoid | | |
| % ≥0.1 IU/mL ^b | 99.4 | 98.7 |
| Anti-tetanus Toxoid | | |
| % ≥0.1 IU/mL ^b | 100 | 98.1 |
| Anti-PT | | |
| % VRc | 98.7 | 95.1 |
| GMC ^b | 48.1 | 28.6 |
| Anti-FHA | | |
| % VRc | 98.7 | 96.5 |
| GMC ^b | 111.9 | 97.6 |
| Anti-pertactin | | |
| % VRc | 91.7 | 95.1 |
| GMC ^b | 95.3 | 80.6 |
| Anti-polio 1 | | |
| % ≥1:8 ^{b,d} | 100 | 100 |
| Anti-polio 2 | | |
| % ≥1:8 ^{b,d} | 100 | 100 |
| Anti-polio 3 | | |
| % ≥1:8 ^{b,d} | 100 | 100 |
| | (n = 114-128) | (n = 111-121) |
| Anti-HBsAge | | |
| %≥10 mIU/mL ^f | 97.7 | 99.2 |
| GMC (mIU/mL) ^f | 1032.1 | 614.5 |

- 498 Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the United States);
- 499 PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).
- Assay methods used: ELISA for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-pertactin,
- and anti-HBsAg; micro-neutralization for anti-polio (1, 2, and 3).
- VR = Vaccine response: In initially seronegative infants, appearance of antibodies (concentration
- 503 ≥5 EL.U./mL); in initially seropositive infants, at least maintenance of pre-vaccination
- 504 concentration.
- 505 GMC = Geometric mean antibody concentration. GMCs are adjusted for pre-vaccination levels.
- ^a One-month blood sampling, range: 20 to 60 days.

- 507 b Seroprotection rate or GMC for PEDIARIX not inferior to separately administered vaccines
- (upper limit of 90% CI on GMC ratio [separate vaccine group/combination vaccine group] <1.5
- for anti-PT, anti-FHA, and anti-pertactin, and upper limit of 95% CI for the difference in
- seroprotection rates [separate vaccine group minus combination vaccine group] <10% for
- diphtheria and tetanus and <5% for the 3 polioviruses). GMCs are adjusted for pre-vaccination
- 512 levels.
- 513 ° The upper limit of 95% CI for differences in vaccine response rates (separate vaccine group
- minus combination group) was 0.31, 1.52, and 9.46 for PT, FHA, and pertactin, respectively.
- No clinical limit defined for non-inferiority.
- 516 ^d Poliovirus-neutralizing antibody titer.
- ^e Subjects who received a previous dose of hepatitis B vaccine were excluded from the analysis
- of hepatitis B seroprotection rates and GMCs presented in the table.
- 519 f No clinical limit defined for non-inferiority.

520 14.3 Concomitant Vaccine Administration

- In a U.S. multicenter study [see Clinical Studies (14.2)], there was no evidence for interference
- with the immune responses to PEDIARIX when administered concomitantly with 7-valent
- 523 pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) relative to 2 weeks prior.
- Anti-PRP (Hib polyribosyl-ribitol-phosphate) seroprotection rates and GMCs of pneumococcal
- antibodies 1 month (range: 20 to 60 days) after the third dose of vaccines for the combination
- vaccine group and the separate vaccine group from the U.S. multicenter study [see Clinical
- 527 Studies (14.2), are presented in Table 4.

- Table 4. Anti-PRP Seroprotection Rates and GMCs (mcg/mL) of Pneumococcal Antibodies
- 529 1 Month^a following the Third Dose of Hib Conjugate Vaccine and Pneumococcal Conjugate
- Vaccine (PCV7) Administered Concomitantly with PEDIARIX or with INFANRIX,
- 531 ENGERIX-B, and IPV

| | PEDIARIX, Hib Vaccine, | INFANRIX, ENGERIX-B, IPV, |
|-----------------------|------------------------|---------------------------|
| | & PCV7 | Hib Vaccine, & PCV7 |
| | (n = 161-168) | (n = 146-156) |
| | % (95% CI) | % (95% CI) |
| Anti-PRP | | |
| ≥0.15 mcg/mL | 100 (97.8, 100) | 99.4 (96.5, 100) |
| Anti-PRP | | |
| ≥1.0 mcg/mL | 95.8 (91.6, 98.3) | 91.0 (85.3, 95.0) |
| | GMC (95% CI) | GMC (95% CI) |
| Pneumococcal Serotype | | |
| 4 | 1.7 (1.5, 2.0) | 2.1 (1.8, 2.4) |
| 6B | 0.8 (0.7, 1.0) | 0.7 (0.5, 0.9) |
| 9V | 1.6 (1.4, 1.8) | 1.6 (1.4, 1.9) |
| 14 | 4.7 (4.0, 5.4) | 6.3 (5.4, 7.4) |
| 18C | 2.6 (2.3, 3.0) | 3.0 (2.5, 3.5) |
| 19F | 1.1 (1.0, 1.3) | 1.1 (0.9, 1.2) |
| 23F | 1.5 (1.2, 1.8) | 1.8 (1.5, 2.3) |

- Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the United States);
- PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).
- Assay method used: ELISA for anti-PRP and 7 pneumococcal serotypes.
- 535 GMC = Geometric mean antibody concentration.
- ^a One-month blood sampling, range: 20 to 60 days.

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558 16 HOW SUPPLIED/STORAGE AND HANDLING

- PEDIARIX is available in 0.5-mL single-dose, disposable, prefilled TIP-LOK syringes
- 560 (packaged without needles):
- 561 NDC 58160-811-43 Syringe in Package of 10: NDC 58160-811-52
- Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
- 563 been frozen.

564 17 PATIENT COUNSELING INFORMATION

- Provide the following information to the parent or guardian:
- Inform of the potential benefits and risks of immunization with PEDIARIX, and of the
- importance of completing the immunization series.
- Inform about the potential for adverse reactions that have been temporally associated with
- administration of PEDIARIX or other vaccines containing similar components.
- Instruct to report any adverse events to their healthcare provider.
- Give the Vaccine Information Statements, which are required by the National Childhood
- Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free
- of charge at the Centers for Disease Control and Prevention (CDC) website
- (www.cdc.gov/vaccines).
- 575 PEDIARIX, INFANRIX, KINRIX, TIP-LOK, and ENGERIX-B are trademarks owned by or
- 576 licensed to the GSK group of companies.

577



| 5/9 | |
|-----|--|
| 580 | Manufactured by GlaxoSmithKline Biologicals |
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| 587 | PDX:XXPI |

EXHIBIT 246

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Pentacel safely and effectively. See full prescribing information for Pentacel.

Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine

Suspension for Intramuscular Injection

Initial U.S. Approval: 2008

----INDICATIONS AND USAGE--

 Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus* influenzae type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to 5th birthday). (1)

--DOSAGE AND ADMINISTRATION-

- The four dose immunization series consists of a 0.5 mL intramuscular injection, after reconstitution, administered at 2, 4, 6 and 15-18 months of age. (2.1)
- Pentacel consists of a liquid vaccine component (DTaP-IPV component) and a lyophilized vaccine component (ActHIB vaccine). Reconstitute the ActHIB vaccine component with the DTaP-IPV component immediately before administration. (2.2)

---DOSAGE FORMS AND STRENGTHS--

 Suspension for injection (0.5 mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single-dose vials. (3)

---CONTRAINDICATIONS-

- Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel, any ingredient of Pentacel, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or H. influenzae type b vaccine. (4.1)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)
- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

---WARNINGS AND PRECAUTIONS-

- Carefully consider benefits and risks before administering Pentacel to persons with a history of:
 - fever ≥40.5°C (≥105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
 - seizures within 3 days after a previous pertussis-containing vaccine.
 (5.2)

- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel. (5.3)
- For infants and children with a history of previous seizures, an antipyretic
 may be administered (in the dosage recommended in its prescribing
 information) at the time of vaccination with Pentacel and for the
 next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.7)

--ADVERSE REACTIONS--

• Rates of adverse reactions varied by dose number. Systemic reactions that occurred in >50% of participants following any dose included fussiness/irritability and inconsolable crying. Fever ≥38.0°C occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in >30% of participants following any dose included tenderness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

----DRUG INTERACTIONS----

- Do not mix Pentacel or any of its components with any other vaccine or diluent. (7.1)
- Immunosuppressive therapies may reduce the immune response to Pentacel. (7.2)
- Urine antigen detection may not have definitive diagnostic value in suspected *H. influenzae* type b disease within one week following Pentacel. (7.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2019

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 - 2.1 Immunization Series
 - 2.2 Administration
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
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 - 4.2 Encephalopathy
 - 4.3 Progressive Neurologic Disorder
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Management of Acute Allergic Reactions
 - 5.2 Adverse Reactions Following Prior Pertussis Vaccination
 - 5.3 Guillain-Barré Syndrome and Brachial Neuritis
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FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

1

7

- 3 Pentacel® is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis,
- 4 poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel is approved
- 5 for use as a four dose series in children 6 weeks through 4 years of age (prior to fifth birthday).

6 2 DOSAGE AND ADMINISTRATION

2.1 Immunization Series

- 8 Pentacel is to be administered as a 4 dose series at 2, 4, 6 and 15-18 months of age. The first dose
- 9 may be given as early as 6 weeks of age. Four doses of Pentacel constitute a primary
- immunization course against pertussis. Three doses of Pentacel constitute a primary immunization
- 11 course against diphtheria, tetanus, *H. influenzae* type b invasive disease, and poliomyelitis; the
- fourth dose is a booster for diphtheria, tetanus, *H. influenzae* type b invasive disease, and
- poliomyelitis immunizations [see Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)].

14 <u>Mixed Sequences of Pentacel and DTaP</u> Vaccine

- While Pentacel and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis
- Vaccine Adsorbed [DTaP], Sanofi Pasteur Limited) vaccines contain the same pertussis antigens,
- manufactured by the same process, Pentacel contains twice the amount of detoxified pertussis
- toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL.
- 19 Pentacel may be used to complete the first 4 doses of the 5-dose DTaP series in infants and
- 20 children who have received 1 or more doses of DAPTACEL and are also scheduled to receive the
- other antigens of Pentacel. However, data are not available on the safety and immunogenicity of
- such mixed sequences of Pentacel and DAPTACEL for successive doses of the primary DTaP
- series. Children who have completed a 4-dose series with Pentacel should receive a fifth dose of
- 24 DTaP vaccine using DAPTACEL at 4-6 years of age. (1)
- 25 Data are not available on the safety and effectiveness of using mixed sequences of Pentacel and
- 26 DTaP vaccine from different manufacturers.

27 Mixed Sequences of Pentacel and IPV Vaccine

- 28 Pentacel may be used in infants and children who have received 1 or more doses of another
- 29 licensed IPV vaccine and are scheduled to receive the antigens of Pentacel. However, data are not
- available on the safety and immunogenicity of Pentacel in such infants and children.
- 31 The Advisory Committee on Immunization Practices (ACIP) recommends that the final dose in
- 32 the 4-dose IPV series be administered at age \geq 4 years. (2) When Pentacel is administered at ages
- 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine should be administered at
- age 4-6 years, resulting in a 5-dose IPV series. (2)

35 Mixed Sequences of Pentacel and Haemophilus b Conjugate Vaccine

- Pentacel may be used to complete the vaccination series in infants and children previously
- vaccinated with one or more doses of Haemophilus b Conjugate Vaccine (either separately
- 38 administered or as part of another combination vaccine), who are also scheduled to receive the
- other antigens of Pentacel. However, data are not available on the safety and immunogenicity of
- 40 Pentacel in such infants and children. If different brands of Haemophilus b Conjugate Vaccines

- are administered to complete the series, three primary immunizing doses are needed, followed by
- 42 a booster dose.

43 **2.2** Administration

- The package contains a vial of the DTaP-IPV component and a vial of lyophilized ActHIB
- 45 vaccine component.
- Before use, thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire
- 47 liquid content and inject into the vial of the lyophilized ActHIB vaccine component. Gently swirl
- 48 the vial now containing Pentacel until a cloudy, uniform, white to off-white (yellow tinge)
- 49 suspension results.

- Parenteral drug products should be inspected visually for particulate matter and discoloration
- 51 prior to administration, whenever solution and container permit. If these conditions exist, Pentacel
- 52 should not be administered.
- Withdraw and administer a single 0.5 mL dose of Pentacel intramuscularly. Pentacel should be
- used immediately after reconstitution. Discard unused portion. Refer to Figures 1, 2, 3, 4 and 5.

56 Pentacel: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV

57 Component



Figure 1
Gently shake the vial of DTaP-IPV component.



Figure 2 Withdraw the entire liquid content.



Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

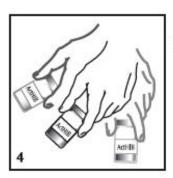


Figure 4
Swirl vial gently.



58 59

60

61

Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly. Pentacel vaccine should be used immediately after reconstitution.

- In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of injection. In older children, the deltoid muscle is usually large enough for injection. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.
- Do not administer this product intravenously or subcutaneously.
- Pentacel should not be mixed in the same syringe with other parenteral products.

65 3 DOSAGE FORMS AND STRENGTHS

- Pentacel is a suspension for injection (0.5 mL dose) supplied as a liquid vaccine component that is
- 67 combined through reconstitution with a lyophilized vaccine component, both in single-dose vials
- [see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)].

69 4 CONTRAINDICATIONS

70 4.1 Hypersensitivity

- A severe allergic reaction (eg. anaphylaxis) after a previous dose of Pentacel or any other
- diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, inactivated poliovirus vaccine
- or *H. influenzae* type b vaccine, or any ingredient of this vaccine is a contraindication to
- administration of Pentacel [see *Description (11)*].

75 4.2 Encephalopathy

- 76 Encephalopathy (eg., coma, decreased level of consciousness, prolonged seizures) within 7 days of
- a previous dose of a pertussis containing vaccine that is not attributable to another identifiable
- 78 cause is a contraindication to administration of any pertussis-containing vaccine, including
- 79 Pentacel.

80 4.3 Progressive Neurologic Disorder

- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive
- 82 encephalopathy is a contraindication to administration of any pertussis-containing vaccine
- 83 including Pentacel. Pertussis vaccine should not be administered to individuals with such
- 84 conditions until a treatment regimen has been established and the condition has stabilized.

85 5 WARNINGS AND PRECAUTIONS

86 5.1 Management of Acute Allergic Reactions

- 87 Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be
- available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

89 5.2 Adverse Reactions Following Prior Pertussis Vaccination

- 90 If any of the following events occur within the specified period after administration of a pertussis
- vaccine, the decision to administer Pentacel should be based on careful consideration of potential
- 92 benefits and possible risks.

95

- Temperature of ≥40.5°C (≥105°F) within 48 hours, not attributable to another identifiable cause.
 - Collapse or shock-like state (hypotonic-hyporesponsive episode (HHE)) within 48 hours.
- Persistent, inconsolable crying lasting ≥3 hours within 48 hours.
- Seizures with or without fever within 3 days.

98 5.3 Guillain-Barré Syndrome and Brachial Neuritis

- A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus
- toxoid and both brachial neuritis and Guillain-Barré syndrome. (3) If Guillain-Barré syndrome
- occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for
- Guillain-Barré syndrome may be increased following Pentacel.

103 5.4 Infants and Children with a History of Previous Seizures

- For infants or children with a history of previous seizures, an appropriate antipyretic may be
- administered (in the dosage recommended in its prescribing information) at the time of
- vaccination with a vaccine containing acellular pertussis antigens (including Pentacel) and for the
- following 24 hours, to reduce the possibility of post-vaccination fever.

108 5.5 Limitations of Vaccine Effectiveness

Vaccination with Pentacel may not protect all individuals.

110 5.6 Altered Immunocompetence

- If Pentacel is administered to immunocompromised persons, including persons receiving
- immunosuppressive therapy, the expected immune response may not be obtained [see *Drug*
- 113 *Interactions* (7.2)].

114 **5.7 Apnea in Premature Infants**

- Apnea following intramuscular vaccination has been observed in some infants born prematurely.
- The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant
- born prematurely should be based on consideration of the individual infant's medical status and
- the potential benefits and possible risks of vaccination.

119 6 ADVERSE REACTIONS

120 6.1 Clinical Trials Experience

- Rates of adverse reactions varied by dose number. The most frequent (>50% of participants)
- systemic reactions following any dose were fussiness/irritability and inconsolable crying. The
- most frequent (>30% of participants) injection site reactions following any dose were tenderness
- and increased circumference of the injected arm.
- Because clinical trials are conducted under widely varying conditions, adverse reaction rates
- observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials
- of another vaccine and may not reflect the rates observed in practice. The adverse reaction
- information from clinical trials does, however, provide a basis for identifying the adverse events
- that appear to be related to vaccine use and for approximating rates of those events.
- The poliovirus component (poliovirus types 1, 2, and 3) of this formulation of Pentacel is grown
- in Vero cells [see *Description (11)*]. The clinical study data in this section were accrued with a
- Pentacel formulation in which the poliovirus component was grown in MRC-5 cells. The safety of
- Pentacel was evaluated in four clinical studies in which a total of 5,980 participants received at
- least one dose of Pentacel. In three of the studies, conducted in the US, a total of 4,198
- participants were enrolled to receive four consecutive doses of Pentacel. In the fourth study,
- 136 conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel
- received a fourth dose. The vaccination schedules of Pentacel, Control vaccines, and
- concomitantly administered vaccines used in these studies are provided in Table 1.
- Across the four studies, 50.8% of participants were female. Among participants in the three US
- studies, 64.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and
- 9.5% were of other racial/ethnic groups. In the two controlled studies, the racial/ethnic
- distribution of participants who received Pentacel and Control vaccines was similar. In the

- 143 Canadian fourth dose study, 86.0% of participants were Caucasian, 1.9% were Black, 0.8% were
- Hispanic, 4.3% were Asian, 2.0% were East Indian, 0.5% were Native Indian, and 4.5% were of
- other racial/ethnic groups.

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Table 1: Clinical Safety Studies of Pentacel: Vaccination Schedules

| Study | Pentacel | Control Vaccines | Concomitantly Administered Vaccines |
|--------|------------------------------|--|--|
| 494-01 | 2, 4, 6 and 15 months | HCPDT + POLIOVAX + ActHIB at 2, 4, 6, and 15 months | 7-valent pneumococcal conjugate vaccine* (PCV7) at 2, 4, and 6 months in a subset of participants† Hepatitis B vaccine at 2 and 6 months‡ |
| P3T06 | 2, 4, 6, and 15-16 months | DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months; and DAPTACEL + ActHIB at 15-16 months | PCV7* at 2, 4, and 6 months Hepatitis B vaccine at 2 and 6 months [‡] |
| 494-03 | 2, 4, 6, and 15-16 months | None | PCV7* at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants Hepatitis B vaccine at 2 and 6 months (if a dose was previously administered) * or at 2, 4, and 6 months (if no previous dose) Measles, mumps, rubella vaccine (MMR) and varicella vaccine at 12 or 15 months in random subsets of participants |
| 5A9908 | 15-18 months [¶] | None | None |

HCPDT: non-US licensed DTaP vaccine that is identical to the DTaP component of Pentacel. POLIOVAX: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited. IPOL: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur SA.

- * PCV7 manufactured by Wyeth Laboratories.
- PCV7 was introduced after the study was initiated, and thus, administered concomitantly with Pentacel vaccine in a subset of participants.
- The first dose of hepatitis B vaccine (manufacturer not specified) was administered prior to study initiation, from birth to 21 days of age. Subsequent doses were with hepatitis B vaccine manufactured by Merck and Co.
- 152 § MMR and varicella vaccines were both manufactured by Merck and Co.
- 153 Study participants previously had received three doses of Pentacel vaccine by 8 months of age.

154 Solicited Adverse Reactions

- 155 The incidence and severity of selected solicited injection site and systemic adverse reactions that
- occurred within 3 days following each dose of Pentacel or Control vaccines in Study P3T06 is
- shown in Table 2. Information on these reactions was recorded daily by parents or guardians on
- diary cards. In Table 2, injection site reactions are reported for the Pentacel and DAPTACEL
- injection sites.

Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by Severity Occurring within 0-3 days
 of Pentacel or Control Vaccines in Study P3T06

| | | | | T | | | |
|-----------------------|--|--|--|---|---|---------------------------|-----------------------|
| | Pen | tacel | | | DAPT | CACEL | |
| Dose 1 N = 465-467 | Dose 2 N = 451 % | Dose 3 N = 438-440 | Dose 4 N = 387-396 | Dose 1 N = 1,400-1,404 | Dose 2 N = 1,358-1,359 % | Dose 3 N = 1,311-1,312 | Dose 4 N = 376-380 |
| | | | | | | | |
| 7.1 | 8.4 | 8.7 | 17.3 | 6.2 | 7.1 | 9.6 | 16.4 |
| 2.8 | 1.8 | 1.8 | 9.2 | 1.0 | 0.6 | 1.9 | 7.9 |
| 0.6 | 0.2 | 0.0 | 2.3 | 0.4 | 0.1 | 0.0 | 2.4 |
| | | | | | | | |
| 7.5 | 7.3 | 5.0 | 9.7 | 4.0 | 4.0 | 6.5 | 10.3 |
| 3.0 | 2.0 | 1.6 | 3.8 | 1.6 | 0.7 | 1.1 | 4.0 |
| 0.9 | 0.0 | 0.0 | 0.8 | 0.4 | 0.1 | 0.1 | 1.3 |
| | | | | | | | |
| 47.5 | 39.2 | 42.7 | 56.1 | 48.8 | 38.2 | 40.9 | 51.1 |
| 19.6 | 10.6 | 11.6 | 16.7 | 20.7 | 12.2 | 12.3 | 15.8 |
| 5.4 | 1.6 | 1.4 | 3.3 | 4.1 | 2.3 | 1.7 | 2.4 |
| - | - | _ | 33.6 4.7 0.5 | _ | - | - | 30.6 6.9 0.8 |
| | Pen | tacel | | DAPT | ACEL + IPOL + A | ActHIB | DAPTACEL + ActHIB |
| Dose 1 N = 466-467 | Dose 2 N = 451-452 % | Dose 3 N = 435-440 | Dose 4 N = 389-398 | Dose 1 N = 1,390-1,406 | Dose 2 N = 1,346-1,360 % | Dose 3 N = 1,301-1,312 | Dose 4 N = 379-381 |
| | | | | | | | |
| 5.8 | 10.9 | 16.3 | 13.4 | 9.3 | 16.1 | 15.8 | 8.7 |
| 1.3 | 2.4 | 4.4 | 5.1 | 1.6 | 4.3 | 5.1 | 3.2 |
| 0.4 | 0.0 | 0.7 | 0.3 | 0.1 | 0.4 | 0.3 | 0.8 |
| | | | | | | | |
| | | | | | | | 24.1 |
| 22.9 | 12.4 0.7 | 12.7 0.2 | 9.8 2.5 | 24.3 | 15.8 1.4 | 12.7 | 9.2 0.3 |
| 2.1 | | | | 1.2 | | 0.6 | |
| | N = 465-467 % 7.1 2.8 0.6 7.5 3.0 0.9 47.5 19.6 5.4 - Dose 1 N = 466-467 % 5.8 1.3 0.4 45.8 22.9 | Dose 1 Dose 2 N = 465-467 N = 451 % % 7.1 8.4 2.8 1.8 0.6 0.2 7.5 7.3 3.0 2.0 0.9 0.0 47.5 39.2 19.6 10.6 5.4 1.6 Pen Pen S.8 10.9 1.3 2.4 0.4 0.0 45.8 22.9 12.4 | N = 465-467 N = 451 N = 438-440 % % % 7.1 8.4 8.7 2.8 1.8 1.8 0.6 0.2 0.0 7.5 7.3 5.0 3.0 2.0 1.6 0.9 0.0 0.0 47.5 39.2 42.7 19.6 10.6 11.6 5.4 1.6 1.4 Pentacel Pentacel See 3 N = 435-440 % % 16.3 1.3 2.4 4.4 0.4 0.0 0.7 45.8 32.7 12.4 12.7 | Dose 1 Dose 2 Dose 3 Dose 4 N = 465-467 N = 451 N = 438-440 N = 387-396 % % % % 7.1 8.4 8.7 17.3 2.8 1.8 1.8 9.2 0.6 0.2 0.0 2.3 7.5 7.3 5.0 9.7 3.0 2.0 1.6 3.8 0.9 0.0 0.0 0.8 47.5 39.2 42.7 56.1 19.6 10.6 11.6 16.7 5.4 1.6 1.4 3.3 - - - 33.6 4.7 0.5 0.5 N = 451-452 N = 435-440 N = 389-398 % % % % % 5.8 10.9 16.3 13.4 1.3 2.4 4.4 5.1 0.4 0.0 0.7 0.3 45.8 32.7 32.5 | Dose 1 N = 465-467 Dose 2 N = 451 Dose 3 N = 438-440 Dose 4 N = 387-396 Dose 1 N = 1,400-1,404 7.1 8.4 8.7 17.3 6.2 2.8 1.8 1.8 9.2 1.0 0.6 0.2 0.0 2.3 0.4 7.5 7.3 5.0 9.7 4.0 3.0 2.0 1.6 3.8 1.6 0.9 0.0 0.0 0.8 0.4 47.5 39.2 42.7 56.1 48.8 19.6 10.6 11.6 16.7 20.7 5.4 1.6 1.4 3.3 4.1 - - - 33.6 - - 4.7 0.5 - - - - Dose 1 N = 466-467 N = 451-452 No N = 435-440 No N = 389-398 No N = 1,390-1,406 No N = 1,390-1,406 No N = 1,390-1,406 No N = 1,290-1,406 No N = | Dose 1 | Dose 1 |

| Inconsolable Crying | | | | | | | | |
|------------------------|------|------|------|------|------|------|------|------|
| Any | 59.3 | 49.8 | 47.3 | 35.9 | 58.5 | 51.4 | 47.9 | 36.2 |
| ≥1 hour | 19.7 | 10.6 | 13.6 | 11.8 | 16.4 | 16.0 | 12.2 | 10.5 |
| >3 hours | 1.9 | 0.9 | 1.1 | 2.3 | 2.2 | 3.4 | 1.4 | 1.8 |
| Fussiness/Irritability | | | | | | | | |
| Any | 76.9 | 71.2 | 68.0 | 53.5 | 75.8 | 70.7 | 67.1 | 53.8 |
| ≥1 hour | 34.5 | 27.0 | 26.4 | 23.6 | 33.3 | 30.5 | 26.2 | 19.4 |
| >3 hours | 4.3 | 4.0 | 5.0 | 5.3 | 5.6 | 5.5 | 4.3 | 4.5 |

^{*} Any: Mild, Moderate or Severe; Mild: subject whimpers when site is touched; Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.

[†] Fever is based upon actual temperatures recorded with no adjustments to the measurement route.

[†] Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 46.0%, 53.0%, 1.0%, and 0% respectively, for Pentacel vaccine and 44.8%, 54.0%, 1.0%, and 0.1%, respectively, for DAPTACEL + IPOL + ActHIB. Following Dose 4, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 62.7%, 34.4%, 2.4% and 0.5%, respectively, for Pentacel vaccine, and 61.1%, 36.6%, 1.7% and 0.5%, respectively, for DAPTACEL + ActHIB.

Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

170 Hypotonic Hyporesponsive Episodes

- 171 In Study P3T06, the diary cards included questions pertaining to HHEs. In Studies 494-01,
- 494-03, and 5A9908, a question about the occurrence of fainting or change in mental status was
- asked during post-vaccination phone calls. Across these 4 studies, no HHEs, as defined in a report
- of a US Public Health Service workshop (4) were reported among participants who received
- Pentacel (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB (N = 1,032) or
- separately administered DAPTACEL + IPOL + ActHIB (N = 1,455). Hypotonia not fulfilling
- 177 HHE criteria within 7 days following vaccination was reported in 4 participants after the
- administration of Pentacel (1 on the same day as the 1st dose; 3 on the same day as the 3rd dose)
- and in 1 participant after the administration of DAPTACEL + IPOL + ActHIB (4 days following
- the 1^{st} dose).

181 Seizures

- Across Studies 494-01, 494-03, 5A9908 and P3T06, a total of 8 participants experienced a seizure
- within 7 days following either Pentacel (4 participants; N = 4,197 for at least one of Doses 1-3;
- N = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB (3 participants;
- N = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4), separately administered
- DAPTACEL + IPOL + ActHIB (1 participant; N = 1,455 for at least one of Doses 1-3), or
- separately administered DAPTACEL + ActHIB (0 participants; N = 418 for Dose 4). Among the
- four participants who experienced a seizure within 7 days following Pentacel, one participant in
- 189 Study 494-01 had an afebrile seizure 6 days after the first dose, one participant in Study 494-01
- had a possible seizure the same day as the third dose, and two participants in Study 5A9908 had a
- 191 febrile seizure 2 and 4 days, respectively, after the fourth dose. Among the four participants who
- experienced a seizure within 7 days following Control vaccines, one participant had an afebrile
- seizure the same day as the first dose of DAPTACEL + IPOL + ActHIB, one participant had an
- afebrile seizure the same day as the second dose of HCPDT + POLIOVAX + ActHIB, and two
- participants had a febrile seizure 6 and 7 days, respectively, after the fourth dose of HCPDT +
- 196 POLIOVAX + ActHIB.

197 Serious Adverse Events

- 198 In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of
- 199 484 (3.9%) participants who received Pentacel and 50 of 1,455 (3.4%) participants who received
- 200 DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following
- Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel and 4
- of 418 (1.0%) participants who received DAPTACEL + ActHIB experienced a serious adverse
- event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control
- 204 vaccines, 23 of 2,506 (0.9%) participants who received Pentacel and 11 of 1,032 (1.1%)
- 205 participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event.
- Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants
- 207 who received Pentacel and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX +
- 208 ActHIB experienced a serious adverse event.
- Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel
- or Control vaccines, overall, the most frequently reported serious adverse events were
- bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03,
- 5A9908 and P3T06, within 30 days following Dose 4 of Pentacel or Control vaccines, overall, the

213 most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and 214 pneumonia. 215 Across Studies 494-01, 494-03, 5A9908 and P3T06, two cases of encephalopathy were reported, both in participants who had received Pentacel (N = 5,979). One case occurred 30 days post-216 vaccination and was secondary to cardiac arrest following cardiac surgery. One infant who had 217 218 onset of neurologic symptoms 8 days post-vaccination was subsequently found to have structural 219 cerebral abnormalities and was diagnosed with congenital encephalopathy. 220 A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9908 and P3T06: 4 in children 221 who had received Pentacel (N = 5,979) and one in a participant who had received DAPTACEL + IPOL + ActHIB (N = 1,455). There were no deaths reported in children who received HCPDT + 222 223 POLIOVAX + ActHIB (N = 1,032). Causes of death among children who received Pentacel were 224 asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (8, 23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died 225 226 secondary to aspiration 222 days following DAPTACEL + IPOL + ActHIB. 6.2 227 **Data from Postmarketing Experience** 228 The following additional adverse events have been spontaneously reported during the 229 post-marketing use of Pentacel worldwide, since 1997. Between 1997 and 2007, Pentacel was 230 primarily used in Canada. Because these events are reported voluntarily from a population of 231 uncertain size, it may not be possible to reliably estimate their frequency or establish a causal 232 relationship to vaccine exposure. 233 The following adverse events were included based on one or more of the following factors: 234 severity, frequency of reporting, or strength of evidence for a causal relationship to Pentacel. 235 Cardiac disorders 236 Cyanosis 237 • Gastrointestinal disorders 238 Vomiting, diarrhea 239 General disorders and administration site conditions 240 Injection site reactions (including inflammation, mass, abscess and sterile abscess), extensive swelling of the injected limb (including swelling that involved adjacent joints), 241 242 vaccination failure/therapeutic response decreased (invasive *H. influenzae* type b disease) 243 • Immune system disorders Anaphylaxis/anaphylactic reaction, hypersensitivity (such as rash and urticaria) 244 245 Infections and infestations Meningitis, rhinitis, viral infection 246 247 Metabolism and nutrition disorders 248 Decreased appetite 249 Nervous system disorders 250 Somnolence, HHE, depressed level of consciousness

| 251252 | • | Psychiatric disorders Screaming |
|---|-----------------------------|---|
| 253 254 | • | Respiratory, thoracic and mediastinal disorders Apnea, cough |
| 255 256 | • | Skin and subcutaneous tissue disorders Erythema, skin discoloration |
| 257 258 | • | Vascular disorders Pallor |
| 259 | 7 | DRUG INTERACTIONS |
| 260 | 7.1 | Concomitant Administration with Other Vaccines |
| 261 262 263 264 265 | license varice at the | tical trials, Pentacel was administered concomitantly with one or more of the following US ed vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and lla vaccines [see <i>Adverse Reactions</i> (6) and <i>Clinical Studies</i> (14)]. When Pentacel is given same time as another injectable vaccine(s), the vaccine(s) should be administered with ent syringes and at different injection sites. |
| 266 | 7.2 | Immunosuppressive Treatments |
| 267268269 | drugs | nosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic and corticosteroids (used in greater than physiologic doses), may reduce the immune use to Pentacel [see <i>Warnings and Precautions</i> (5.6)]. |
| 270 | 7.3 | Drug/Laboratory Test Interactions |
| 271272273 | detect | enuria has been detected in some instances following receipt of ActHIB. Urine antigen ion may not have definite diagnostic value in suspected <i>H. influenzae</i> type b disease within eek following receipt of Pentacel. (5) |
| 274 | 8 | USE IN SPECIFIC POPULATIONS |
| 275 | 8.4 | Pediatric Use |
| 276 277 278 279 280 281 | month (14)]. suppo | afety and effectiveness of Pentacel was established in the age group 6 weeks through 18 as on the basis of clinical studies [see <i>Clinical Trials Experience</i> (6.1) and <i>Clinical Studies</i> The safety and effectiveness of Pentacel in the age group 19 months through 4 years is read by evidence in children 6 weeks through 18 months. The safety and effectiveness of cel in infants less than 6 weeks of age and in children 5 to 16 years of age have not been ished. |

11 DESCRIPTION

- 283 Pentacel consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and
- Inactivated Poliovirus (DTaP-IPV) component and an ActHIB® component combined through
- reconstitution for intramuscular injection. ActHIB (Haemophilus b Conjugate Vaccine [Tetanus
- Toxoid Conjugate]), consists of *H. influenzae* type b capsular polysaccharide
- 287 (polyribosyl-ribitol-phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T). The DTaP-
- 288 IPV component is supplied as a sterile liquid used to reconstitute the lyophilized ActHIB
- component to form Pentacel. Pentacel is a uniform, cloudy, white to off-white (yellow tinge)
- suspension.

- 291 Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis
- antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA),
- 293 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], inactivated polioviruses
- 294 [29 D-antigen units (DU) Type 1 (Mahoney), 7 DU Type 2 (MEF-1), 26 DU Type 3 (Saukett)]
- and 10 mcg PRP of *H. influenzae* type b covalently bound to 24 mcg of tetanus toxoid (PRP-T).
- Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as
- 297 the adjuvant, <8.1 mcg polysorbate 80, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a
- preservative), 42.5 mg sucrose, 2 mcg to 7 mcg residual formaldehyde, <50 ng residual
- 299 glutaraldehyde, ≤10 ng residual bovine serum albumin, <0.0001 pg streptomycin sulphate, <0.01
- pg of neomycin and <0.000001 pg polymyxin B sulphate.
- 301 Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (6) After
- purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with
- 303 formaldehyde and diafiltered.
- 304 Clostridium tetani is grown in modified Mueller-Miller casamino acid medium without beef
- heart infusion. (7) Tetanus toxin is detoxified with formaldehyde and purified by ammonium
- 306 sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed
- onto aluminum phosphate.
- The acellular pertussis vaccine antigens are produced from *Bordetella pertussis* cultures grown
- in Stainer-Scholte medium (8) modified by the addition of casamino acids and dimethyl-beta-
- 310 cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium.
- FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by
- sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with
- 313 glutaraldehyde. FHA is treated with formaldehyde and the residual aldehydes are removed by
- 314 ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.
- 315 The Type 1, Type 2, and Type 3 polioviruses are individually grown in Vero cells (a continuous
- line of monkey kidney cells). Prior to viral propagation, the cells are grown in Iscove's medium,
- supplemented with calf serum. For viral propagation, the culture medium is replaced by M199
- 318 medium without calf serum. The viral harvests are concentrated and purified, then inactivated
- with formaldehyde to produce monovalent suspensions of each serotype. Specified quantities of
- 320 monovalent suspensions of each serotype are mixed to produce the trivalent poliovirus
- 321 concentrate. The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with
- aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for

- 323 injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the
- 324 DTaP-IPV component is diluted to its final concentration. The DTaP-IPV component does not
- 325 contain a preservative.
- Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig
- potency test. The potency of the acellular pertussis antigens is evaluated by the antibody
- 328 response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-
- 329 linked immunosorbent assay (ELISA). The potency of inactivated poliovirus antigens is
- determined by measuring antibody-mediated neutralization of poliovirus in sera from immunized
- 331 rats.
- PRP, a high molecular weight polymer, is prepared from the *Haemophilus influenzae* type b
- strain 1482 grown in a semi-synthetic medium. (9) The tetanus toxoid for conjugation to PRP is
- prepared by ammonium sulfate purification, and formalin inactivation of the toxin from cultures
- of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (10) The
- toxoid is filter sterilized prior to the conjugation process. The ActHIB component does not
- contain a preservative. Potency of the ActHIB component is specified on each lot by limits on
- 338 the content of PRP polysaccharide and protein per dose and the proportion of polysaccharide and
- protein that is characterized as high molecular weight conjugate.
- The vial stoppers for the DTaP-IPV and ActHIB components of Pentacel are not made with
- natural rubber latex.

342 12 CLINICAL PHARMACOLOGY

343 **12.1 Mechanism of Action**

- 344 Diphtheria
- Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*.
- Protection against disease is due to the development of neutralizing antibodies to diphtheria
- toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree
- of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (11)
- Levels of 1.0 IU/mL have been associated with long-term protection. (12)
- 350 <u>Tetanus</u>
- 351 Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*.
- Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A
- serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is
- 354 considered the minimum protective level. (11) (13) A tetanus antitoxoid level ≥0.1 IU/mL as
- measured by the ELISA used in clinical studies of Pentacel is considered protective.

356 Pertussis

- Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative
- coccobacillus produces a variety of biologically active components, though their role in either
- 359 the pathogenesis of, or immunity to, pertussis has not been clearly defined.

360 Poliomyelitis

- Polioviruses, of which there are three serotypes (Types 1, 2, and 3) are enteroviruses. The
- presence of poliovirus type-specific neutralizing antibodies has been correlated with protection
- against poliomyelitis. (14)

364 Invasive Disease Due to H. influenzae Type b

- 365 *H. influenzae* type b can cause invasive disease such as meningitis and sepsis. Anti-PRP antibody
- has been shown to correlate with protection against invasive disease due to *H. influenzae* type b.
- Based on data from passive antibody studies (15) and an efficacy study with *H. influenzae* type b
- polysaccharide vaccine in Finland, (16) a post-vaccination anti-PRP level of 0.15 mcg/mL has
- been accepted as a minimal protective level. Data from an efficacy study with *H. influenzae* type
- b polysaccharide vaccine in Finland indicate that a level >1.0 mcg/mL 3 weeks after vaccination
- predicts protection through a subsequent one-year period. (17) (18) These levels have been used
- to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB
- 373 component of Pentacel.

374 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Pentacel has not been evaluated for carcinogenic or mutagenic potential or impairment of

377 fertility.

378 14 CLINICAL STUDIES

- 379 The efficacy of Pentacel is based on the immunogenicity of the individual antigens compared to
- separately administered vaccines. The poliovirus component (poliovirus types 1, 2 and 3) of this
- formulation of Pentacel is grown in Vero cells [see *Description (11)*]. The clinical study data in
- this section were accrued with a Pentacel formulation in which the poliovirus component was
- grown in MRC-5 cells. The poliovirus component of the two Pentacel formulations are
- analytically comparable. Serological correlates of protection exist for diphtheria, tetanus,
- poliomyelitis, and invasive disease due to *H. influenzae* type b [see *Clinical Pharmacology*]
- 386 (12.1)]. The efficacy against pertussis, for which there is no well-established serological
- correlate of protection, was based, in part, on a comparison of pertussis immune responses
- following Pentacel in US children to responses following DAPTACEL (Diphtheria and Tetanus
- 389 Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) manufactured by Sanofi Pasteur
- 390 Limited) in an efficacy study conducted in Sweden (Sweden I Efficacy Trial). While Pentacel
- and DAPTACEL contain the same pertussis antigens, manufactured by the same process,
- Pentacel contains twice as much detoxified PT and four times as much FHA as DAPTACEL.
- 393 Immune responses to Pentacel were evaluated in four US studies: Studies 494-01, P3T06, 494-
- 394 03, and M5A10. The vaccination schedules of Pentacel, Control vaccines, and concomitantly
- administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in Table 1 [see

- 396 Clinical Trials Experience (6.1)]. In Study M5A10, participants were randomized to receive
- Pentacel or separately administered DAPTACEL, IPOL, and ActHIB at 2, 4, and 6 months of
- age. 7-valent pneumococcal conjugate (PCV7, Wyeth Pharmaceuticals Inc.) at 2, 4, and 6
- months of age, and Hepatitis B vaccine (Merck and Co. or GlaxoSmithKline Biologicals) at 2
- and 6 months of age, were administered concomitantly with Pentacel or Control vaccines.

401 14.1 Diphtheria

- The proportions of participants achieving diphtheria antitoxin seroprotective levels one month
- 403 following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in
- 404 Table 3.

405

14.2 Tetanus

- The proportions of participants achieving tetanus antitoxoid seroprotective levels one month
- following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in Table 3.
- Table 3: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month
- 410 Following Dose 3 and Dose 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Children
- Vaccinated at 2, 4, 6, and 15-16 Months of Age

| | Pentacel | DAPTACEL + IPOL + ActHIB |
|----------------------------|-------------|-----------------------------|
| Post-Dose 3 | N = 331-345 | N = 1,037-1,099 |
| Diphtheria Antitoxin | | |
| % ≥0.01 IU/mL* | 100.0% | 100.0% |
| % ≥0.10 IU/mL [†] | 98.8% | 98.5% |
| Tetanus Antitoxoid | | |
| % ≥0.10 IU/mL [†] | 99.7% | 100.0% |
| Post-Dose 4 | N = 341-352 | N = 328-334 |
| Diphtheria Antitoxin | | |
| % ≥0.10 IU/mL* | 100.0% | 100.0% |
| % ≥1.0 IU/mL [†] | 96.5% | 95.7% |
| Tetanus Antitoxoid | | |
| % ≥0.10 IU/mL* | 100.0% | 100.0% |
| % ≥1.0 IU/mL ^{†‡} | 92.9% | 99.4% |
| | | |

⁴¹² Per Protocol Immunogenicity population.

^{*} Seroprotection rate following Pentacel vaccine is not inferior to DAPTACEL vaccine (upper limit of 90% CI of the difference DAPTACEL – Pentacel is <10%).

Non-inferiority criteria were not pre-specified.

With the ELISA used in this study, a tetanus antitoxoid level of 1.0 IU/mL is 10 times the protective level.

14.3 Pertussis

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- In a clinical pertussis vaccine efficacy study conducted in Sweden during 1992-1995
- 419 (Sweden I Efficacy Trial), 2,587 infants received DAPTACEL and 2,574 infants received a non-
- 420 US licensed DT vaccine as placebo at 2, 4, and 6 months of age. (1) The mean length of follow-
- 421 up was 2 years after the third dose of vaccine. The protective efficacy of DAPTACEL against
- 422 pertussis after 3 doses of vaccine using the World Health Organization (WHO) case
- definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or
- 424 epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1%,
- 425 88.6%). The protective efficacy of DAPTACEL against mild pertussis (≥1 day of cough with
- laboratory confirmation) was 77.9% (95% CI 72.6%, 82.2%). Protection against pertussis by
- DAPTACEL was sustained for the 2-year follow-up period.
- Based on comparisons of the immune responses to DAPTACEL in US infants (Post-Dose 3) and
- Canadian children (Post-Dose 4) relative to infants who participated in the Sweden I Efficacy
- 430 Trial, it was concluded that 4 doses of DAPTACEL were needed for primary immunization
- against pertussis in US children. (1)
- In a serology bridging analysis, immune responses to FHA, PRN and FIM in a subset of infants
- 433 who received three doses of DAPTACEL in the Sweden I Efficacy Trial were compared to the
- Post-Dose 3 and Post-Dose 4 responses in a subset of US children from Study 494-01 who
- received Pentacel (Table 4). Available stored sera from infants who received DAPTACEL in the
- Sweden I Efficacy Trial and sera from children who received PCV7 concomitantly with the first
- 437 three doses of Pentacel in Study 494-01 (Table 1) were assayed in parallel. Data on levels of
- antibody to PT using an adequately specific assay were not available for this serology bridging
- 439 analysis.

- 440 Geometric mean antibody concentrations (GMCs) and seroconversion rates for antibodies to
- 441 FHA, PRN and FIM one month following Dose 3 of DAPTACEL in the subset of infants from
- the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel in a subset
- of infants from US Study 494-01 are presented in Table 4. Seroconversion was defined as 4-fold
- rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). For anti-FHA and
- anti-FIM, the non-inferiority criteria were met for seroconversion rates, and for anti-FHA, anti-
- PRN, and anti-FIM, the non-inferiority criteria were met for GMCs, following Dose 4 of
- Pentacel relative to Dose 3 of DAPTACEL. The non-inferiority criterion for anti-PRN
- seroconversion following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL was not met
- [upper limit of 95% CI for difference in rate (DAPTACEL minus Pentacel) = 13.24%]. Whether
- 450 the lower anti-PRN seroconversion rate following Dose 4 of Pentacel in US children relative to
- Dose 3 of DAPTACEL in Swedish infants correlates with diminished efficacy of Pentacel
- against pertussis is unknown.

- Table 4: FHA, PRN and FIM Antibody Responses One Month Following Dose 3 of
- DAPTACEL in a Subset of Infants Vaccinated at 2, 4, and 6 Months of Age in the Sweden I
- 456 Efficacy Trial and One Month Following Dose 3 and Dose 4 of Pentacel in a Subset of
- 457 Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in US Study 494-01

| | Post-Dose 3 DAPTACEL Sweden I Efficacy Trial N = 80 | Post-Dose 3 Pentacel* US Study 494-01 N = 730-995 | Post-Dose 4 Pentacel† US Study 494-01 N = 507-554 |
|--------------------------------------|---|---|---|
| Anti-FHA | | | |
| % achieving 4-fold rise [‡] | 68.8 | 79.8 | 91.7§ |
| GMC (EU/mL) | 40.70 | 71.46 | 129.85§ |
| Anti-PRN | | | |
| % achieving 4-fold rise [‡] | 98.8 | 74.4 | 89.2 [¶] |
| GMC (EU/mL) | 111.26 | 38.11 | 90.82§ |
| Anti-FIM | | | |
| % achieving 4-fold rise [‡] | 86.3 | 86.5 | 91.5§ |
| GMC (EU/mL) | 339.31 | 265.02 | 506.57 [§] |

Analyzed sera were from subsets of the Per Protocol Immunogenicity populations in each study. Data on anti-PT levels using an adequately specific assay were not available.

- * Non-inferiority criteria were not pre-specified for the comparisons of immune responses to Pentacel vaccine Post-Dose 3 vs. DAPTACEL vaccine Post-Dose 3.
 - † Pre-specified non-inferiority analyses compared immune responses to Pentacel vaccine Post-Dose 4 vs. DAPTACEL vaccine Post-Dose 3.
- Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.
 - Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine is not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) <10% and upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5].
 - Non-inferiority criterion is not met for percent achieving 4-fold rise in anti-PRN Post-Dose 4 Pentacel vaccine relative to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) = 13.24%, exceeds the non-inferiority criterion of <10%].

In a separate study, Study P3T06, US infants were randomized to receive either Pentacel or DAPTACEL + IPOL + ActHIB at 2, 4, 6, and 15-16 months of age (Table 1). The pertussis immune responses (GMCs and seroconversion rates) one month following the third and fourth doses were compared between the two groups (Table 5). Seroconversion was defined as a 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). Data on anti-PT responses obtained from an adequately specific assay were available on only a non-random subset of study participants. The subset of study participants was representative of all study participants with regard to Pre-Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to

- participants with regard to Pre-Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to FHA, PRN and FIM. For each of the pertussis antigens, non-inferiority criteria were met for
- 478 seroconversion rates and GMCs following Dose 3 of Pentacel relative to Dose 3 of DAPTACEL.
- Following Dose 4 of Pentacel relative to Dose 4 of DAPTACEL, non-inferiority criteria were
- 480 met for all comparisons except for anti-PRN GMCs [upper limit of 90% CI for ratio of GMCs
- (DAPTACEL/Pentacel) = 2.25]. Whether the lower anti-PRN GMC following Dose 4 of
- (DAFTACEL/FEIRace) 2.23]. Whether the lower anti-FRN GMC following Dose 4 of
- Pentacel relative to Dose 4 of DAPTACEL in US children correlates with diminished efficacy of
- 483 Pentacel against pertussis is unknown.

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Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in Study P3T06

| | Post-Dose 3 Pentacel | Post-Dose 3 DAPTACEL + IPOL + ActHIB | Post-Dose 4 Pentacel | Post-Dose 4 DAPTACEL + ActHIB |
|---|--|--|---|-------------------------------------|
| | N = 143 | N = 481-485 | N = 113 | N = 127-128 |
| Anti-PT | | | | |
| % achieving 4-fold rise* | 95.8^{\dagger} | 87.3 | 93.8‡ | 91.3 |
| GMC (EU/mL) | 102.62^{\dagger} | 61.88 | 107.89‡ | 100.29 |
| | | | | |
| | N = 218-318 | N = 714-1,016 | N = 230-367 | N = 237-347 |
| Anti-FHA % achieving 4-fold rise* GMC (EU/mL) | 81.9 [§] 73.68 [§] | 60.9 29.22 | 88.4¶ 107.94¶ | 79.3 64.02 |
| Anti-PRN % achieving 4-fold rise* GMC (EU/mL) | 74.2 [§] 36.05 [§] | 75.4 43.25 | 92.7 [¶] 93.59 [#] | 98.3 186.07 |
| Anti-FIM % achieving 4-fold rise* GMC (EU/mL) | 91.7 [§] 268.15 [§] | 86.3 267.18 | 93.5¶ 553.39¶ | 91.6 513.54 |

Per Protocol Immunogenicity population for anti-FHA, anti-PRN, and anti-FIM.

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- Non-random subset of per Protocol Immunogenicity population for anti-PT. See text for further information on the subset evaluated.
- * Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.
- Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].
- Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].
- Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].
- Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].
- Non-inferiority criterion is not met for GMC Post-Dose 4 Pentacel vaccine relative to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) = 2.25, which exceeds the non-inferiority criterion of <1.5].

14.4 Poliomyelitis

- In Study P3T06 (Table 1), in which infants were randomized to receive the first three doses of
- Pentacel or DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months of age, one month following
- the third dose of study vaccines, ≥99.4% of participants in both groups
- 510 (Pentacel: N = 338-350), (DAPTACEL + IPOL + ActHIB: N = 1,050-1,097) achieved
- neutralizing antibody levels of ≥ 1.8 for Poliovirus types 1, 2, and 3.
- In Study 494-01 (Table 1), in which infants were randomized to receive Pentacel or HCPDT +
- POLIOVAX + ActHIB, GMTs (1/dil) of antibodies to Poliovirus types 1, 2, and 3 one month
- following Dose 4 of Pentacel (N = 851-857) were 2,304, 4,178, and 4,415, respectively, and one
- 515 month following Dose 4 of POLIOVAX (N = 284-287) were 2,330, 2,840, and 3,300,
- 516 respectively.

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14.5 Invasive Disease due to H. Influenzae Type b

- Anti-PRP seroprotection rates and GMCs one month following Dose 3 of Pentacel or separately
- administered ActHIB in studies 494-01, P3T06, and M5A10 are presented in Table 6. In Study
- 520 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an
- anti-PRP level ≥1.0 mcg/mL and for anti-PRP GMCs following Pentacel compared with
- separately administered ActHIB. In each of Studies P3T06 and M5A10, the non-inferiority
- criterion was met for the proportion of participants who achieved an anti-PRP level ≥ 1.0
- mcg/mL following Pentacel compared with separately administered ActHIB. In Study M5A10,
- 525 the non-inferiority criterion was met for anti-PRP GMCs following Pentacel compared with
- 526 separately administered ActHIB.

Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of Pentacel or Separate DTaP + IPV + ActHIB Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and M5A10

| | Study 494-01 | |
|-----------------------------------|--------------------|-----------------------------------|
| | Pentacel N = 1,127 | HCPDT + POLIOVAX + ActHIB N = 401 |
| % achieving anti-PRP ≥0.15 mcg/mL | 95.4* | 98.3 |
| % achieving anti-PRP ≥1.0 mcg/mL | 79.1 [†] | 88.8 |
| Anti-PRP GMC (mcg/mL) | 3.19‡ | 6.23 |
| | Study P3T06 | |
| | Pentacel | DAPTACEL + IPOL + |
| | N=365 | ActHIB |
| | | N = 1,128 |
| % achieving anti-PRP ≥0.15 mcg/mL | 92.3* | 93.3 |
| % achieving anti-PRP ≥1.0 mcg/mL | 72.1* | 70.8 |
| Anti-PRP GMC (mcg/mL) | 2.31§ | 2.29 |
| | Study M5A10 | |
| | Pentacel | DAPTACEL + IPOL + |
| | N = 826 | ActHIB |
| | | N = 421 |
| % achieving anti-PRP ≥0.15 mcg/mL | 93.8¶ | 90.3 |
| % achieving anti-PRP ≥1.0 mcg/mL | 75.1 [¶] | 74.8 |
| Anti-PRP GMC (mcg/mL) | 2.52 # | 2.38 |

Per Protocol Immunogenicity population for all studies.

IPV indicates Poliovirus Vaccine Inactivated.

- * Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel) <10%].
- Non-inferiority criterion not met for percent achieving anti-PRP ≥1.0 mcg/mL following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel), 12.9%, exceeds the non-inferiority criterion <10%].
- Non-inferiority criterion not met for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel), 2.26, exceeds the non-inferiority criterion <1.5].
- Non-inferiority criterion not pre-specified.
- Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 95% CI for difference in rates (ActHIB minus Pentacel) <10%].
- GMC following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI of GMC ratio (ActHIB/Pentacel) <1.5].
- In Study 494-01, at 15 months of age prior to receipt of Dose 4 of study vaccines, 68.6% of
- Pentacel recipients (N = 829) and 80.8% of separately administered ActHIB recipients (N = 276)
- had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 98.2% of Pentacel
- recipients (N = 874) and 99.0% of separately administered ActHIB recipients (N = 291) had an
- 547 anti-PRP level \geq 1.0 mcg/mL.
- In Study P3T06, at 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of
- Pentacel recipients (N = 335) and 60.7% of separately administered ActHIB recipients (N = 323)

- had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel
- recipients (N = 361) and 95.9% of separately administered ActHIB recipients (N = 340) had an
- anti-PRP level \geq 1.0 mcg/mL.

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14.6 Concomitantly Administered Vaccines

- In Study P3T06, (Table 1) there was no evidence for reduced antibody responses to hepatitis B
- vaccine (percent of participants with anti-HBsAg ≥10 mIU/mL and GMCs) or PCV7 (percent of
- participants with antibody levels \geq 0.15 mcg/mL and \geq 0.5 mcg/mL and GMCs to each serotype)
- administered concomitantly with Pentacel (N = 321-325) relative to these vaccines administered
- concomitantly with DAPTACEL + IPOL + ActHIB (N = 998-1,029). The immune responses to
- hepatitis B vaccine and PCV7 were evaluated one month following the third dose.
- In Study 494-03, (Table 1) there was no evidence for interference in the immune response to the
- fourth dose of PCV7 (percent of participants with antibody levels ≥ 0.15 mcg/mL and ≥ 0.5
- mcg/mL and GMCs to each serotype) administered at 15 months of age concomitantly with
- Pentacel (N = 155) relative to this vaccine administered concomitantly with MMR and varicella
- vaccines (N = 158). There was no evidence for interference in the immune response to MMR and
- varicella vaccines (percent of participants with pre-specified seroresponse level) administered at
- 566 15 months of age concomitantly with Pentacel (N = 154) relative to these vaccines administered
- 567 concomitantly with PCV7 (N = 144). The immune responses to MMR, varicella vaccine and the
- fourth dose of PCV7 were evaluated one month post-vaccination.

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613 16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

- The vial stoppers for the DTaP-IPV and ActHIB vaccine components of Pentacel are not made
- with natural rubber latex.

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- 5 Dose Package (NDC No. 49281-511-05) containing 5 vials of DTaP-IPV component (NDC
- No. 49281-561-01) to be used to reconstitute 5 single-dose vials of lyophilized ActHIB vaccine
- 619 component (NDC No. 49281-544-58).

621 **16.2 Storage and Handling**

- Pentacel should be stored at 2° to 8°C (35° to 46°F). Do not freeze. Product which has been
- exposed to freezing should not be used. Do not use after expiration date shown on the label.

624 17 PATIENT COUNSELING INFORMATION

- Before administration of Pentacel, health-care personnel should inform the parent or guardian of
- the benefits and risks of the vaccine and the importance of completing the immunization series
- unless a contraindication to further immunization exists.

| 628 629 630 631 632 633 | The health-care provider should inform the parent or guardian about the potential for adverse reactions that have been temporally associated with Pentacel or other vaccines containing similar ingredients. The health-care provider should provide the Vaccine Information Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each immunization. The parent or guardian should be instructed to report adverse reactions to their health-care provider. |
|--|--|
| 634 | Manufactured by: |
| 635 | Sanofi Pasteur Limited |
| 636 | Toronto Ontario Canada |
| 637 | and Sanofi Pasteur SA |
| 638 | Marcy L'Etoile France |
| | |
| 639 | Distributed by: |
| 640 | Sanofi Pasteur Inc. |
| 641 | Swiftwater PA 18370 USA |
| 642 | Pentacel® is a registered trademark of Sanofi Pasteur, its affiliates and subsidiaries. |
| 643 | R0-1219 USA |
| | SANOFI PASTEUR 🗳 |
| 644 | SANOFI PASIEUR |
| \cup TT | |

EXHIBIT 247

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These highlights do not include all the information needed to use HAVRIX safely and effectively. See full prescribing information for HAVRIX.

HAVRIX (Hepatitis A Vaccine) Suspension for Intramuscular Injection Initial U.S. Approval: 1995

-----INDICATIONS AND USAGE -----

HAVRIX is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV). HAVRIX is approved for use in persons 12 months of age and older. Primary immunization should be administered at least 2 weeks prior to expected exposure to HAV. (1)

----- DOSAGE AND ADMINISTRATION ------

- HAVRIX is administered by intramuscular injection. (2.2)
- Children and adolescents: A single 0.5-mL dose and a 0.5-mL booster dose administered between 6 to 12 months later. (2.3)
- Adults: A single 1-mL dose and a 1-mL booster dose administered between 6 to 12 months later. (2.3)

--- DOSAGE FORMS AND STRENGTHS -----

- Suspension for injection available in the following presentations:
- 0.5-mL single-dose vials and prefilled syringes. (3)
- 1-mL single-dose vials and prefilled syringes. (3)

-----CONTRAINDICATIONS ----

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis A-containing vaccine, or to any component of HAVRIX, including neomycin. (4)

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including HAVRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

----- ADVERSE REACTIONS -----

- In studies of adults and children 2 years of age and older, the most common solicited adverse events were injection-site soreness (56% of adults and 21% of children) and headache (14% of adults and less than 9% of children). (6.1)
- In studies of children 11 to 25 months of age, the most frequently reported solicited local reactions were pain (32%) and redness (29%). Common solicited general adverse events were irritability (42%), drowsiness (28%), and loss of appetite (28%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

------DRUG INTERACTIONS ------

Do not mix HAVRIX with any other vaccine or product in the same syringe or vial. (7.1)

---- USE IN SPECIFIC POPULATIONS -----

Safety and effectiveness of HAVRIX have not been established in pregnant women and nursing mothers. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: X/201X

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FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

- 3 HAVRIX® is indicated for active immunization against disease caused by hepatitis A virus
- 4 (HAV). HAVRIX is approved for use in persons 12 months of age and older. Primary
- 5 immunization should be administered at least 2 weeks prior to expected exposure to HAV.

6 2 DOSAGE AND ADMINISTRATION

7 2.1 Preparation for Administration

- 8 Shake well before use. With thorough agitation, HAVRIX is a homogeneous, turbid, white
- 9 suspension. Do not administer if it appears otherwise. Parenteral drug products should be
- 10 inspected visually for particulate matter and discoloration prior to administration, whenever
- solution and container permit. If either of these conditions exists, the vaccine should not be
- 12 administered.

1

- 13 For the prefilled syringes, attach a sterile needle and administer intramuscularly.
- 14 For the vials, use a sterile needle and sterile syringe to withdraw the vaccine dose and administer
- intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a
- recipient is not necessary unless the needle has been damaged or contaminated. Use a separate
- sterile needle and syringe for each individual.

18 **2.2 Administration**

- 19 HAVRIX should be administered by intramuscular injection only. HAVRIX should not be
- administered in the gluteal region; such injections may result in suboptimal response.
- 21 Do not administer this product intravenously, intradermally, or subcutaneously.

22 **2.3** Recommended Dose and Schedule

23 Children and Adolescents

- 24 Primary immunization for children and adolescents (12 months through 18 years of age) consists
- of a single 0.5-mL dose and a 0.5-mL booster dose administered anytime between 6 and
- 26 12 months later. The preferred sites for intramuscular injections are the anterolateral aspect of
- 27 the thigh in young children or the deltoid muscle of the upper arm in older children.
- 28 Adults
- 29 Primary immunization for adults consists of a single 1-mL dose and a 1-mL booster dose
- administered anytime between 6 and 12 months later. In adults, the injection should be given in
- 31 the deltoid region.

2

32 3 DOSAGE FORMS AND STRENGTHS

- 33 Suspension for injection available in the following presentations:
- 0.5-mL single-dose vials and prefilled TIP-LOK® syringes.
- 1-mL single-dose vials and prefilled TIP-LOK syringes. [See How Supplied/Storage and
- 36 *Handling (16).*]

37 4 CONTRAINDICATIONS

- 38 Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis A-containing
- 39 vaccine, or to any component of HAVRIX, including neomycin, is a contraindication to
- 40 administration of HAVRIX [see Description (11)].

41 5 WARNINGS AND PRECAUTIONS

- 42 **5.1** Latex
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic
- 44 reactions.
- 45 **5.2 Syncope**
- 46 Syncope (fainting) can occur in association with administration of injectable vaccines, including
- 47 HAVRIX. Syncope can be accompanied by transient neurological signs such as visual
- disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to
- 49 avoid falling injury and to restore cerebral perfusion following syncope.

50 5.3 Preventing and Managing Allergic Vaccine Reactions

- 51 Appropriate medical treatment and supervision must be available to manage possible
- anaphylactic reactions following administration of the vaccine [see Contraindications (4)].

53 **5.4 Altered Immunocompetence**

- 54 Immunocompromised persons may have a diminished immune response to HAVRIX, including
- 55 individuals receiving immunosuppressant therapy.

56 5.5 Limitations of Vaccine Effectiveness

- 57 Hepatitis A virus has a relatively long incubation period (15 to 50 days). HAVRIX may not
- 58 prevent hepatitis A infection in individuals who have an unrecognized hepatitis A infection at the
- 59 time of vaccination. Additionally, vaccination with HAVRIX may not protect all individuals.

60 6 ADVERSE REACTIONS

61 6.1 Clinical Trials Experience

- Because clinical trials are conducted under widely varying conditions, adverse reaction rates
- observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical
- trials of another vaccine, and may not reflect the rates observed in practice.
- 65 The safety of HAVRIX has been evaluated in 61 clinical trials involving approximately 37,000
- individuals receiving doses of 360 EL.U. (n = 21,928 in 3- or 4-dose schedule), 720 EL.U.
- (n = 12,274 in 2- or 3-dose schedule), or 1440 EL.U. (n = 2,782 in 2- or 3-dose schedule).
- Of solicited adverse events in clinical trials of adults, who received HAVRIX 1440 EL.U., and
- children (2 years of age and older), who received either HAVRIX 360 EL.U. or 720 EL.U., the
- most frequently reported was injection-site soreness (56% of adults and 21% of children); less
- 71 than 0.5% of soreness was reported as severe. Headache was reported by 14% of adults and less
- than 9% of children. Other solicited and unsolicited events occurring during clinical trials are
- 73 listed below.
- 74 <u>Incidence 1% to 10% of Injections</u>
- 75 Metabolism and Nutrition Disorders: Anorexia.
- 76 Gastrointestinal Disorders: Nausea.
- 77 General Disorders and Administration Site Conditions: Fatigue, fever >99.5°F (37.5°C),
- 78 induration, redness, and swelling of the injection site; malaise.
- 79 Incidence <1% of Injections
- 80 *Infections and Infestations:* Pharyngitis, upper respiratory tract infections.
- 81 Blood and Lymphatic System Disorders: Lymphadenopathy.
- 82 *Psychiatric Disorders:* Insomnia.
- 83 *Nervous System Disorders:* Dysgeusia, hypertonia.
- 84 Eye Disorders: Photophobia.
- 85 Ear and Labyrinth Disorders: Vertigo.
- 86 Gastrointestinal Disorders: Abdominal pain, diarrhea, vomiting.
- 87 Skin and Subcutaneous Tissue Disorders: Pruritus, rash, urticaria.
- 88 Musculoskeletal and Connective Tissue Disorders: Arthralgia, myalgia.
- 89 General Disorders and Administration Site Conditions: Injection site hematoma.
- 90 *Investigations:* Creatine phosphokinase increased.

- 91 Coadministration Studies of HAVRIX in Children 11 to 25 Months of Age
- In 4 studies, 3,152 children 11 to 25 months of age received at least one dose of HAVRIX
- 720 EL.U. administered alone or concomitantly with other routine childhood vaccinations [see
- 94 Clinical Studies (14.2, 14.5)]. The studies included HAV 210 (N = 1,084), HAV 232 (N = 394),
- 95 HAV 220 (N = 433), and HAV 231 (N = 1,241).
- In the largest of these studies (HAV 231) conducted in the US, 1,241 children 15 months of age
- 97 were randomized to receive: Group 1) HAVRIX alone; Group 2) HAVRIX concomitantly with
- 98 measles, mumps, and rubella (MMR) vaccine (manufactured by Merck and Co.) and varicella
- 99 vaccine (manufactured by Merck and Co.); or Group 3) MMR and varicella vaccines. Subjects in
- 100 Group 3 who received MMR and varicella vaccines received the first dose of HAVRIX 42 days
- later. A second dose of HAVRIX was administered to all subjects 6 to 9 months after the first
- dose of HAVRIX. Solicited local adverse reactions and general events were recorded by
- parents/guardians on diary cards for 4 days (days 0 to 3) after vaccination. Unsolicited adverse
- events were recorded on the diary card for 31 days after vaccination. Telephone follow-up was
- 105 conducted 6 months after the last vaccination to inquire about serious adverse events, new onset
- 106 chronic illnesses and medically significant events. A total of 1,035 children completed the 6-
- month follow-up. Among subjects in all groups combined, 53% were male; 69% of subjects were
- white, 16% were Hispanic, 9% were black and 6% were other racial/ethnic groups.
- 109 Percentages of subjects with solicited local adverse reactions and general adverse events
- following HAVRIX administered alone (Group 1) or concomitantly with MMR and varicella
- vaccines (Group 2) are presented in Table 1. The solicited adverse events from the 3 additional
- 112 coadministration studies conducted with HAVRIX were comparable to those from Study
- 113 HAV 231.

- 114 Table 1. Solicited Local Adverse Reactions and General Adverse Events occurring within
- 4 Days of Vaccination^a in Children 15 to 24 Months of Age with HAVRIX Administered
- 116 Alone or Concomitantly with MMR and Varicella Vaccines (TVC)

| | Group 1 HAVRIX Dose 1 % | Group 2 HAVRIX+ MMR+V ^b Dose 1 | Group 1 HAVRIX Dose 2 % | Group 2 HAVRIX Dose 2 % |
|----------------------------|----------------------------------|--|----------------------------------|----------------------------------|
| Local (at injection site | for HAVRIX) | | | |
| N | 298 | 411 | 272 | 373 |
| Pain, any | 23.8 | 23.6 | 24.3 | 30.3 |
| Redness, any | 20.1 | 20.0 | 22.8 | 23.9 |
| Swelling, any | 8.7 | 10.2 | 9.6 | 9.9 |
| General | | | | |
| N | 300 | 417 | 271 | 375 |
| Irritability, any | 33.3 | 43.9 | 31.0 | 27.2 |
| Irritability, grade 3 | 0.3 | 1.9 | 1.5 | 0.3 |
| Drowsiness, any | 22.3 | 35.3 | 21.0 | 20.8 |
| Drowsiness, grade 3 | 1.0 | 2.2 | 1.1 | 0.0 |
| Loss of appetite, any | 18.3 | 26.1 | 19.9 | 20.5 |
| Loss of appetite, grade 3 | 1.0 | 1.4 | 0.4 | 0.3 |
| Fever ≥100.6°F (38.1°C) | 3.0 | 4.8 | 3.3 | 2.7 |
| Fever ≥101.5°F (38.6°C) | 2.0 | 2.6 | 1.8 | 1.6 |
| Fever ≥102.4°F (39.1°C) | 0.7 | 0.7 | 0.4 | 1.1 |

- 117 Total vaccinated cohort (TVC) = all subjects who received at least one dose of vaccine.
- N = number of subjects who received at least one dose of vaccine and for whom diary card information was available.
- Grade 3: drowsiness defined as prevented normal daily activities; irritability/fussiness defined as crying that could not be comforted/prevented normal daily activities; loss of appetite defined as no eating at all.
- ^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.
- b MMR = measles, mumps, and rubella vaccine; V = varicella vaccine.
- Serious Adverse Events in Children 11 to 25 Months of Age: Among these 4 studies, 0.9%
- 126 (29/3,152) of subjects reported a serious adverse event within the 31-day period following
- vaccination with HAVRIX. Among subjects administered HAVRIX alone 1.0% (13/1,332)

- reported a serious adverse event. Among subjects who received HAVRIX concomitantly with
- other childhood vaccines, 0.9% (8/909) reported a serious adverse event. In these 4 studies, there
- were 4 reports of seizure within 31 days post-vaccination: these occurred 2, 9, and 27 days
- following the first dose of HAVRIX administered alone and 12 days following the second dose
- of HAVRIX. In one subject who received INFANRIX and Hib conjugate vaccine followed by
- HAVRIX 6 weeks later, bronchial hyperreactivity and respiratory distress were reported on the
- day of administration of HAVRIX alone.

135 **6.2 Postmarketing Experience**

- In addition to reports in clinical trials, worldwide voluntary reports of adverse events received
- for HAVRIX since market introduction of this vaccine are listed below. This list includes serious
- adverse events or events which have a suspected causal connection to components of HAVRIX
- or other vaccines or drugs. Because these events are reported voluntarily from a population of
- uncertain size, it is not always possible to reliably estimate their frequency or establish a causal
- relationship to the vaccine.
- 142 Infections and Infestations
- 143 Rhinitis.
- 144 Blood and Lymphatic System Disorders
- 145 Thrombocytopenia.
- 146 Immune System Disorders
- 147 Anaphylactic reaction, anaphylactoid reaction, serum sickness–like syndrome.
- 148 Nervous System Disorders
- 149 Convulsion, dizziness, encephalopathy, Guillain-Barré syndrome, hypoesthesia, multiple
- sclerosis, myelitis, neuropathy, paresthesia, somnolence, syncope.
- 151 <u>Vascular Disorders</u>
- 152 Vasculitis.
- 153 Respiratory, Thoracic, and Mediastinal Disorders
- 154 Dyspnea.
- 155 <u>Hepatobiliary Disorders</u>
- 156 Hepatitis, jaundice.
- 157 Skin and Subcutaneous Tissue Disorders
- 158 Angioedema, erythema multiforme, hyperhidrosis.
- 159 Congenital, Familial, and Genetic Disorders
- 160 Congenital anomaly.

- 161 <u>Musculoskeletal and Connective Tissue Disorders</u>
- 162 Musculoskeletal stiffness.
- 163 General Disorders and Administration Site Conditions
- 164 Chills, influenza-like symptoms, injection site reaction, local swelling.

165 7 DRUG INTERACTIONS

166 7.1 Concomitant Administration with Vaccines and Immune Globulin

- In clinical studies HAVRIX was administered concomitantly with the following vaccines [see
- 168 Adverse Reactions (6.1) and Clinical Studies (14.5)]:
- INFANRIX (DTaP);
- Hib conjugate vaccine;
- pneumococcal 7-valent conjugate vaccine;
- MMR vaccine;
- varicella vaccine.
- 174 HAVRIX may be administered concomitantly with immune globulin.
- 175 When concomitant administration of other vaccines or immune globulin is required, they should
- be given with different syringes and at different injection sites. Do not mix HAVRIX with any
- other vaccine or product in the same syringe or vial.

178 **7.2** Immunosuppressive Therapies

- 179 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
- drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune
- response to HAVRIX.

182 8 USE IN SPECIFIC POPULATIONS

- **183 8.1 Pregnancy**
- 184 Pregnancy Category C
- Animal reproduction studies have not been conducted with HAVRIX. It is also not known
- 186 whether HAVRIX can cause fetal harm when administered to a pregnant woman or can affect
- reproduction capacity. HAVRIX should be given to a pregnant woman only if clearly needed.

188 **8.3 Nursing Mothers**

- 189 It is not known whether HAVRIX is excreted in human milk. Because many drugs are excreted
- in human milk, caution should be exercised when HAVRIX is administered to a nursing woman.

191 **8.4 Pediatric Use**

- The safety and effectiveness of HAVRIX, doses of 360 EL.U. or 720 EL.U., have been evaluated
- in more than 22,000 subjects 1 year to 18 years of age.
- 194 The safety and effectiveness of HAVRIX have not been established in subjects younger than
- 195 12 months of age.

196 8.5 Geriatric Use

- 197 Clinical studies of HAVRIX did not include sufficient numbers of subjects 65 years of age and
- older to determine whether they respond differently from younger subjects. Other reported
- 199 clinical experience has not identified differences in overall safety between these subjects and
- 200 younger adult subjects.

201 8.6 Hepatic Impairment

- 202 Subjects with chronic liver disease had a lower antibody response to HAVRIX than healthy
- subjects [see Clinical Studies (14.3)].

204 11 DESCRIPTION

- 205 HAVRIX (Hepatitis A Vaccine) is a sterile suspension of inactivated virus for intramuscular
- administration. The virus (strain HM175) is propagated in MRC-5 human diploid cells. After
- removal of the cell culture medium, the cells are lysed to form a suspension. This suspension is
- 208 purified through ultrafiltration and gel permeation chromatography procedures. Treatment of this
- 209 lysate with formalin ensures viral inactivation. Viral antigen activity is referenced to a standard
- using an enzyme linked immunosorbent assay (ELISA), and is therefore expressed in terms of
- 211 ELISA Units (EL.U.).
- Each 1-mL adult dose of vaccine contains 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of
- aluminum as aluminum hydroxide.
- Each 0.5-mL pediatric dose of vaccine contains 720 EL.U. of viral antigen, adsorbed onto
- 215 0.25 mg of aluminum as aluminum hydroxide.
- 216 HAVRIX contains the following excipients: Amino acid supplement (0.3% w/v) in a
- 217 phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). From the manufacturing
- process, HAVRIX also contains residual MRC-5 cellular proteins (not more than 5 mcg/mL),
- formalin (not more than 0.1 mg/mL), and neomycin sulfate (not more than 40 ng/mL), an
- aminoglycoside antibiotic included in the cell growth media.
- HAVRIX is formulated without preservatives.
- HAVRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes
- 223 contain natural rubber latex; the plungers are not made with natural rubber latex. The vial
- stoppers are not made with natural rubber latex.

225 12 CLINICAL PHARMACOLOGY

226 **12.1 Mechanism of Action**

- The hepatitis A virus belongs to the picornavirus family. It is one of several hepatitis viruses that
- cause systemic disease with pathology in the liver.
- The incubation period for hepatitis A averages 28 days (range: 15 to 50 days). The course of
- 230 hepatitis A infection is extremely variable, ranging from asymptomatic infection to icteric
- hepatitis and death.
- The presence of antibodies to HAV confers protection against hepatitis A infection. However,
- 233 the lowest titer needed to confer protection has not been determined.

234 13 NONCLINICAL TOXICOLOGY

235 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

- 236 HAVRIX has not been evaluated for its carcinogenic potential, mutagenic potential, or potential
- for impairment of fertility.

238 14 CLINICAL STUDIES

239 14.1 Pediatric Effectiveness Studies

- 240 Protective efficacy with HAVRIX has been demonstrated in a double-blind, randomized
- controlled study in school children (age 1 to 16 years) in Thailand who were at high risk of HAV
- infection. A total of 40,119 children were randomized to be vaccinated with either HAVRIX
- 243 360 EL.U. or ENGERIX-B 10 mcg at 0, 1, and 12 months. Of these, 19,037 children received 2
- 244 doses of HAVRIX (0 and 1 months) and 19,120 children received 2 doses of control vaccine,
- ENGERIX-B (0 and 1 months). A total of 38,157 children entered surveillance at day 138 and
- were observed for an additional 8 months. Using the protocol-defined endpoint (≥2 days absence
- 247 from school, ALT level >45 U/mL, and a positive result in the HAVAB-M test), 32 cases of
- clinical hepatitis A occurred in the control group. In the HAVRIX group, 2 cases were identified.
- These 2 cases were mild in terms of both biochemical and clinical indices of hepatitis A disease.
- 250 Thus the calculated efficacy rate for prevention of clinical hepatitis A was 94% (95% Confidence
- 251 Interval [CI]: 74, 98).
- In outbreak investigations occurring in the trial, 26 clinical cases of hepatitis A (of a total of 34
- occurring in the trial) occurred. No cases occurred in vaccinees who received HAVRIX.
- Using additional virological and serological analyses post hoc, the efficacy of HAVRIX was
- confirmed. Up to 3 additional cases of mild clinical illness may have occurred in vaccinees.
- Using available testing, these illnesses could neither be proven nor disproven to have been
- caused by HAV. By including these as cases, the calculated efficacy rate for prevention of
- 258 clinical hepatitis A would be 84% (95% CI: 60, 94).

259 14.2 Immunogenicity in Children and Adolescents

- 260 Immune Response to HAVRIX 720 EL.U./0.5 mL at 11 to 25 Months of Age (Study
- 261 HAV 210)
- In this prospective, open-label, multicenter study, 1,084 children were administered study
- vaccine in one of 5 groups:
- 264 (1) Children 11 to 13 months of age who received HAVRIX on a 0- and 6-month schedule;
- 265 (2) Children 15 to 18 months of age who received HAVRIX on a 0- and 6-month schedule;
- 266 (3) Children 15 to 18 months of age who received HAVRIX coadministered with INFANRIX
- and Haemophilus b (Hib) conjugate vaccine (no longer US-licensed) at month 0 and HAVRIX at
- 268 month 6;
- 269 (4) Children 15 to 18 months of age who received INFANRIX coadministered with Hib
- 270 conjugate vaccine at month 0 and HAVRIX at months 1 and 7;
- 271 (5) Children 23 to 25 months of age who received HAVRIX on a 0- and 6-month schedule.
- Among subjects in all groups, 52% were male; 61% of subjects were white, 9% were black, 3%
- were Asian, and 27% were other racial/ethnic groups. The anti-hepatitis A antibody vaccine
- 274 responses and GMTs, calculated on responders for groups 1, 2, and 5 are presented in Table 2.
- Vaccine response rates were similar among the 3 age groups that received HAVRIX. One month
- after the second dose of HAVRIX, the GMT in each of the younger age groups (11 to 13 and 15
- 277 to 18 months of age) was shown to be similar to that achieved in the 23 to 25 months of age
- 278 group.

Table 2. Anti-Hepatitis A Immune Response following 2 Doses of HAVRIX

280 720 EL.U./0.5 mL Administered 6 Months Apart in Children Given the First Dose of

281 HAVRIX at 11 to 13 Months of Age, 15 to 18 Months of Age, or 23 to 25 Months of Age

| | | Vaccine Response | | GMT |
|------------------------|-----|------------------|---------|--------------------|
| Age group | N | % | 95% CI | (mIU/mL) |
| 11-13 months (Group 1) | 218 | 99 | 97, 100 | 1,461 ^a |
| 15-18 months (Group 2) | 200 | 100 | 98, 100 | 1,635 ^a |
| 23-25 months (Group 5) | 211 | 100 | 98, 100 | 1,911 |

- Vaccine response = Seroconversion (anti-HAV ≥15 mIU/mL [lower limit of antibody
- measurement by assay]) in children initially seronegative or at least the maintenance of the
- pre-vaccination anti-HAV concentration in initially seropositive children.
- 285 CI = Confidence Interval; GMT = Geometric mean antibody titer.
- 286 a Calculated on vaccine responders one month post-dose 2. GMTs in children 11 to 13 months
- of age and 15 to 18 months of age were non-inferior (similar) to the GMT in children 23 to
- 288 25 months of age (i.e., the lower limit of the two-sided 95% CI on the GMT ratio for
- Group 1/Group 5 and for Group 2/Group 5 were both ≥ 0.5).

- 290 In 3 additional clinical studies (HAV 232, HAV 220, and HAV 231), children received either 2
- doses of HAVRIX alone or the first dose of HAVRIX concomitantly administered with other
- 292 routinely recommended US-licensed vaccines followed by a second dose of HAVRIX. After the
- second dose of HAVRIX, there was no evidence for interference with the anti-HAV response in
- 294 the children who received concomitantly administered vaccines compared to those who received
- 295 HAVRIX alone. [See Adverse Reactions (6.1) and Clinical Studies (14.5).]
- 296 Immune Response to HAVRIX 360 EL.U. among Individuals 2 to 18 Years of Age
- In 6 clinical studies, 762 subjects 2 to 18 years of age received 2 doses of HAVRIX (360 EL.U.)
- 298 given 1 month apart (GMT ranged from 197 to 660 mIU/mL). Ninety-nine percent of subjects
- seroconverted following 2 doses. When a third dose of HAVRIX 360 EL.U. was administered
- 300 6 months following the initial dose, all subjects were seropositive (anti-HAV ≥20 mIU/mL)
- 1 month following the third dose, with GMTs rising to a range of 3,388 to 4,643 mIU/mL. In
- 302 1 study in which children were followed for an additional 6 months, all subjects remained
- 303 seropositive.
- Immune Response to HAVRIX 720 EL.U./0.5 mL among Individuals 2 to 19 Years of
- 305 Age
- 306 In 4 clinical studies, 314 children and adolescents ranging from 2 to 19 years of age were
- immunized with 2 doses of HAVRIX 720 EL.U./0.5 mL given 6 months apart. One month after
- the first dose, seroconversion (anti-HAV ≥20 mIU/mL [lower limit of antibody measurement by
- assay]) ranged from 96.8% to 100%, with GMTs of 194 mIU/mL to 305 mIU/mL. In studies in
- which sera were obtained 2 weeks following the initial dose, seroconversion ranged from 91.6%
- 311 to 96.1%. One month following the booster dose at month 6, all subjects were seropositive, with
- 312 GMTs ranging from 2,495 mIU/mL to 3,644 mIU/mL.
- In an additional study in which the booster dose was delayed until 1 year following the initial
- dose, 95.2% of the subjects were seropositive just prior to administration of the booster dose.
- One month later, all subjects were seropositive, with a GMT of 2,657 mIU/mL.
- 316 14.3 Immunogenicity in Adults
- More than 400 healthy adults 18 to 50 years of age in 3 clinical studies were given a single
- 318 1440 EL.U. dose of HAVRIX. All subjects were seronegative for hepatitis A antibodies at
- baseline. Specific humoral antibodies against HAV were elicited in more than 96% of subjects
- when measured 1 month after vaccination. By day 15, 80% to 98% of vaccinees had already
- 321 seroconverted (anti-HAV ≥20 mIU/mL [lower limit of antibody measurement by assay]). GMTs
- of seroconverters ranged from 264 to 339 mIU/mL at day 15 and increased to a range of 335 to
- 323 637 mIU/mL by 1 month following vaccination.
- 324 The GMTs obtained following a single dose of HAVRIX are at least several times higher than
- that expected following receipt of immune globulin.

- In a clinical study using 2.5 to 5 times the standard dose of immune globulin (standard
- dose = 0.02 to 0.06 mL/kg), the GMT in recipients was 146 mIU/mL at 5 days
- post-administration, 77 mIU/mL at month 1, and 63 mIU/mL at month 2.
- In 2 clinical trials in which a booster dose of 1440 EL.U. was given 6 months following the
- initial dose, 100% of vaccinees (n = 269) were seropositive 1 month after the booster dose, with
- 331 GMTs ranging from 3,318 mIU/mL to 5,925 mIU/mL. The titers obtained from this additional
- dose approximate those observed several years after natural infection.
- In a subset of vaccinees (n = 89), a single dose of HAVRIX 1440 EL.U. elicited specific
- anti-HAV neutralizing antibodies in more than 94% of vaccinees when measured 1 month after
- vaccination. These neutralizing antibodies persisted until month 6. One hundred percent of
- vaccinees had neutralizing antibodies when measured 1 month after a booster dose given at
- 337 month 6.
- 338 Immunogenicity of HAVRIX was studied in subjects with chronic liver disease of various
- etiologies. 189 healthy adults and 220 adults with either chronic hepatitis B (n = 46), chronic
- hepatitis C (n = 104), or moderate chronic liver disease of other etiology (n = 70) were
- vaccinated with HAVRIX 1440 EL.U. on a 0- and 6-month schedule. The last group consisted of
- alcoholic cirrhosis (n = 17), autoimmune hepatitis (n = 10), chronic hepatitis/cryptogenic
- cirrhosis (n = 9), hemochromatosis (n = 2), primary biliary cirrhosis (n = 15), primary sclerosing
- cholangitis (n = 4), and unspecified (n = 13). At each time point, geometric mean antibody titers
- 345 (GMTs) were lower for subjects with chronic liver disease than for healthy subjects. At month 7,
- the GMTs ranged from 478 mIU/mL (chronic hepatitis C) to 1,245 mIU/mL (healthy). One
- month after the first dose, seroconversion rates in adults with chronic liver disease were lower
- 348 than in healthy adults. However, 1 month after the booster dose at month 6, seroconversion rates
- were similar in all groups; rates ranged from 94.7% to 98.1%. The relevance of these data to the
- duration of protection afforded by HAVRIX is unknown.
- In subjects with chronic liver disease, local injection site reactions with HAVRIX were similar
- among all 4 groups, and no serious adverse events attributed to the vaccine were reported in
- 353 subjects with chronic liver disease.

354 **14.4 Duration of Immunity**

- 355 The duration of immunity following a complete schedule of immunization with HAVRIX has
- not been established.

357 14.5 Immune Response to Concomitantly Administered Vaccines

- 358 In 3 clinical studies HAVRIX was administered concomitantly with other routinely
- recommended US-licensed vaccines: Study HAV 232: Diphtheria and tetanus toxoids and
- acellular pertussis vaccine adsorbed (INFANRIX, DTaP) and Haemophilus b (Hib) conjugate
- vaccine (tetanus toxoid conjugate) (manufactured by sanofi pasteur SA); Study HAV 220:

- 362 Pneumococcal 7-valent conjugate vaccine (PCV-7) (manufactured by Pfizer), and Study 363 HAV 231: MMR and varicella vaccines. [See Adverse Reactions (6.1).] 364 Concomitant Administration with DTaP and Hib Conjugate Vaccine (Study HAV 232) 365 In this US multicenter study, 468 subjects, children 15 months of age were randomized to 366 receive: Group 1) HAVRIX coadministered with INFANRIX and Hib conjugate vaccine 367 (n = 127); Group 2) INFANRIX and Hib conjugate vaccine alone followed by a first dose of 368 HAVRIX one month later (n = 132); or Group 3) HAVRIX alone (n = 135). All subjects 369 received a second dose of HAVRIX alone 6 to 9 months following the first dose. Among 370 subjects in all groups combined, 53% were male; 64% of subjects were white, 12% were black, 371 6% were Hispanic, and 18% were other racial/ethnic groups. 372 There was no evidence for reduced antibody response to diphtheria and tetanus toxoids 373 (percentage of subjects with antibody levels ≥0.1 mIU/mL to each antigen), pertussis antigens 374 (percentage of subjects with seroresponse, antibody concentrations ≥5 EL.U./mL in seronegative 375 subjects or post-vaccination antibody concentration ≥2 times the pre-vaccination antibody 376 concentration in seropositive subjects, and GMTs), or Hib (percentage of subjects with antibody 377 levels ≥1 mcg/mL to polyribosyl-ribitol phosphate, PRP) when HAVRIX was administered 378 concomitantly with INFANRIX and Hib conjugate vaccine (Group 1) relative to INFANRIX and 379 Hib conjugate vaccine administered together (Group 2). 380 Concomitant Administration with Pneumococcal 7-Valent Conjugate Vaccine (Study 381 HAV 220) 382 In this US multicenter study, 433 children 15 months of age were randomized to receive: 383 Group 1) HAVRIX coadministered with PCV-7 vaccine (n = 137); Group 2) HAVRIX 384 administered alone (n = 147); or Group 3) PCV-7 vaccine administered alone (n = 149) followed 385 by a first dose of HAVRIX one month later. All subjects received a second dose of HAVRIX 6 386 to 9 months after the first dose. Among subjects in all groups combined, 53% were female; 61% 387 of subjects were white, 16% were Hispanic, 15% were black, and 8% were other racial/ethnic 388 groups. 389 There was no evidence for reduced antibody response to PCV-7 (GMC to each serotype) when 390 HAVRIX was administered concomitantly with PCV-7 vaccine (Group 1) relative to PCV-7 391 administered alone (Group 3). 392 Concomitant Administration with MMR and Varicella Vaccines (Study HAV 231)
- 393 In a US multicenter study, there was no evidence for interference in the immune response to
- 394 MMR and varicella vaccines (the percentage of subjects with pre-specified
- 395 seroconversion/seroresponse levels) administered at 15 months of age concomitantly with
- 396 HAVRIX relative to the response when MMR and varicella vaccines are administered without
- 397 HAVRIX. [See Adverse Reactions (6.1).]

398 15 REFERENCES

- 399 1. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or
- 400 passive immunization: Recommendations of the Immunization Practices Advisory
- 401 Committee (ACIP). *MMWR* 2006;55(RR-7):1-23.

402 16 HOW SUPPLIED/STORAGE AND HANDLING

- 403 HAVRIX is available in single-dose vials and prefilled disposable TIP-LOK syringes (packaged
- 404 without needles) (Preservative Free Formulation):
- 405 720 EL.U./0.5 mL
- 406 NDC 58160-825-01 Vial in Package of 10: NDC 58160-825-11
- 407 NDC 58160-825-43 Syringe in Package of 10: NDC 58160-825-52
- 408 1440 EL.U./mL
- 409 NDC 58160-826-01 Vial in Package of 10: NDC 58160-826-11
- 410 NDC 58160-826-05 Syringe in Package of 1: NDC 58160-826-34
- 411 NDC 58160-826-43 Syringe in Package of 10: NDC 58160-826-52
- Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
- been frozen. Do not dilute to administer.

414 17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients and parents or guardians of the potential benefits and risks of
- 416 immunization with HAVRIX.
- Emphasize, when educating vaccine recipients and parents or guardians regarding potential
- side effects, that HAVRIX contains non-infectious killed viruses and cannot cause hepatitis
- 419 A infection.
- Instruct vaccine recipients and parents or guardians to report any adverse events to their
- 421 healthcare provider.
- Give vaccine recipients and parents or guardians the Vaccine Information Statements, which
- are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to
- immunization. These materials are available free of charge at the Centers for Disease Control
- and Prevention (CDC) website (www.cdc.gov/vaccines).
- 427 HAVRIX, ENGERIX-B, INFANRIX, and TIP-LOK are registered trademarks of the GSK group
- 428 of companies.

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EXHIBIT 248

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VAQTA safely and effectively. See full prescribing information for VAQTA.

VAQTA[®] (Hepatitis A Vaccine, Inactivated) Suspension for Intramuscular Injection Initial U.S. Approval: 1996

-----INDICATIONS AND USAGE -----

VAQTA is a vaccine indicated for the prevention of disease caused by hepatitis A virus (HAV) in persons 12 months of age and older. The primary dose should be given at least 2 weeks prior to expected exposure to HAV. (1.1)

----- DOSAGE AND ADMINISTRATION -----

- For intramuscular administration only. (2)
- Children/Adolescents: vaccination consists of a 0.5-mL primary dose administered intramuscularly, and a 0.5-mL booster dose administered intramuscularly 6 to 18 months later. (2.1)
- Adults: vaccination consists of a 1-mL primary dose administered intramuscularly, and a 1-mL booster dose administered intramuscularly 6 to 18 months later. (2.1)

--- DOSAGE FORMS AND STRENGTHS ---

Suspension supplied in four presentations:

- 0.5-mL pediatric dose in single-dose vials and prefilled syringes.
 (3 11 16)
- 1-mL adult dose in single-dose vials and prefilled syringes. (3, 11, 16)

-----CONTRAINDICATIONS -----

Do not administer VAQTA to individuals with a history of immediate and/or severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis A vaccine or with an anaphylactic reaction to neomycin. (4, 11)

---- WARNINGS AND PRECAUTIONS ------

 The vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber that may cause allergic reactions in latex-sensitive individuals. (5.2)

----- ADVERSE REACTIONS -----

The most common local adverse reactions and systemic adverse events (≥15%) reported in different clinical trials across different age groups when VAQTA was administered alone or concomitantly were:

- Children 12 through 23 months of age: injection-site pain/tenderness (37.0%), injection-site erythema (21.2%), fever (16.4% when administered alone, and 27.0% when administered concomitantly) (6.1)
- Children/Adolescents 2 through 18 years of age: injection-site pain (18.7%) (6.1)
- Adults 19 years of age and older: injection-site pain, tenderness, or soreness (67.0%), injection-site warmth (18.2%) and headache (16.1%) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

--- DRUG INTERACTIONS ---

 Do not mix VAQTA with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indications and Use

VAQTA® [Hepatitis A Vaccine, Inactivated] is indicated for the prevention of disease caused by hepatitis A virus (HAV) in persons 12 months of age and older. The primary dose should be given at least 2 weeks prior to expected exposure to HAV.

2 DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION ONLY.

2.1 Dosage and Schedule

Children/Adolescents (12 months through 18 years of age): The vaccination schedule consists of a primary 0.5-mL dose administered intramuscularly, and a 0.5-mL booster dose administered intramuscularly 6 to 18 months later.

Adults (19 years of age and older): The vaccination schedule consists of a primary 1-mL dose administered intramuscularly, and a 1-mL booster dose administered intramuscularly 6 to 18 months later.

Booster Immunization Following Another Manufacturer's Hepatitis A Vaccine: A booster dose of VAQTA may be given at 6 to 12 months following a primary dose of HAVRIX [see Clinical Studies (14.6)].

2.2 Preparation and Administration

Shake the single-dose vial or single-dose prefilled syringe well to obtain a slightly opaque, white suspension before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the suspension does not appear homogenous or if extraneous particulate matter remains or discoloration is observed.

For single-dose vials, withdraw and administer entire dose of VAQTA intramuscularly using a sterile needle and syringe.

For single-dose prefilled syringes, securely attach a needle by twisting in a clockwise direction and administer dose of VAQTA intramuscularly.

For adults, adolescents, and children older than 2 years of age, the deltoid muscle is the preferred site for intramuscular injection. For children 12 through 23 months of age, the anterolateral area of the thigh is the preferred site for intramuscular injection.

3 DOSAGE FORMS AND STRENGTHS

Suspension for injection available in four presentations:

- 0.5-mL pediatric dose in single-dose vials and prefilled syringes
- 1-mL adult dose in single-dose vials and prefilled syringes

[See Description (11) for listing of vaccine components and How Supplied/Storage and Handling (16).]

4 CONTRAINDICATIONS

Do not administer VAQTA to individuals with a history of immediate and/or severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis A vaccine, or to individuals who have had an anaphylactic reaction to any component of VAQTA, including neomycin [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Prevention and Management of Allergic Vaccine Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine [see Contraindications (4)].

5.2 Hypersensitivity to Latex

The vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber that may cause allergic reactions in latex-sensitive individuals [see How Supplied/Storage and Handling (16)].

5.3 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished immune response to VAQTA and may not be protected against HAV infection after vaccination [see Use in Specific Populations (8.6)].

5.4 Limitations of Vaccine Effectiveness

Hepatitis A virus has a relatively long incubation period (approximately 20 to 50 days). VAQTA may not prevent hepatitis A infection in individuals who have an unrecognized hepatitis A infection at the time of vaccination. Vaccination with VAQTA may not result in a protective response in all susceptible vaccinees.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of VAQTA has been evaluated in over 10,000 subjects 1 year to 85 years of age. Subjects were given one or two doses of the vaccine. The second (booster dose) was given 6 months or more after the first dose.

The most common local adverse reactions and systemic adverse events (≥15%) reported in different clinical trials across different age groups when VAQTA was administered alone or concomitantly were:

- Children 12 through 23 months of age: injection-site pain/tenderness (37.0%), injection-site erythema (21.2%), fever (16.4% when administered alone, and 27.0% when administered concomitantly).
- Children/Adolescents 2 through 18 years of age: injection-site pain (18.7%)
- Adults 19 years of age and older: injection-site pain, tenderness, or soreness (67.0%), injection-site warmth (18.2%) and headache (16.1%)

Allergic Reactions

Local and/or systemic allergic reactions that occurred in <1% of over 10,000 children/adolescents or adults in clinical trials regardless of causality included: injection-site pruritus and/or rash; bronchial constriction; asthma; wheezing; edema/swelling; rash; generalized erythema; urticaria; pruritus; eye irritation/itching; dermatitis [see Contraindications (4) and Warnings and Precautions (5.1)].

Children — 12 through 23 Months of Age

Across five clinical trials, 4374 children 12 to 23 months of age received one or two 25U doses of VAQTA, including 3885 children who received 2 doses of VAQTA and 1250 children who received VAQTA concomitantly with one or more other vaccines, including Measles, Mumps, and Rubella Virus Vaccine, Live (M-M-R II®), Varicella Vaccine, Live (VARIVAX®), Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (Tripedia or INFANRIX), Measles, Mumps, Rubella, and Varicella Vaccine, Live (ProQuad®), Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇, Prevnar), or Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate, PedvaxHIB®). Overall, the race distribution of study subjects was as follows: 64.7% Caucasian; 15.7% Hispanic-American; 12.3% Black; 4.8% other; 1.4% Asian; and 1.1% Native American. The distribution of subjects by gender was 51.8% male and 48.2% female.

In an open-label clinical trial, 653 children 12 to 23 months of age were randomized to receive a first dose of VAQTA with ProQuad and Prevnar concomitantly (N=330) or a first dose of ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly, followed by a first dose of VAQTA 6 weeks later (N=323). Approximately 6 months later, subjects received either the second doses of ProQuad and VAQTA concomitantly or the second doses of ProQuad and VAQTA separately. The race distribution of the study subjects was as follows: 60.3% Caucasian; 21.6% African-American; 9.5% Hispanic-American; 7.2% other; 1.1% Asian; and 0.3% Native American. The distribution of subjects by gender was 50.7% male and 49.3% female.

Table 1 presents rates of solicited local reactions at the VAQTA injection site and rates of elevated temperatures (≥100.4°F and ≥102.2°F) that occurred within 5 days following each dose of VAQTA and elevated temperatures >98.6°F for a total of 14 days after vaccination; occurrences of these events were recorded daily on diary cards. Table 2 presents rates of unsolicited systemic adverse events that occurred within 14 days at ≥5% in any group following each dose of VAQTA.

Table 1: Incidences of Solicited Local Adverse Reactions at the VAQTA Injection Site and Elevated Temperatures
Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly With
ProQuad and PREVNAR*

| | Dose 1 | | Dose | 2 |
|--|--------|-------|-------------|-------------------------------|
| Adverse reaction: Days 1-5 unless noted | | | VAQTA alone | VAQTA + ProQuad concomitantly |
| Injection site adverse reactions | N=274 | N=311 | N=251 | N=263 |
| Injection site erythema | 11.7% | 9.6% | 12.7% | 9.5% |
| Injection site pain/tenderness | 15.3% | 20.9% | 20.3% | 17.5% |
| Injection site swelling | 9.5% | 6.8% | 7.6% | 6.1% |
| Temperature > 98.6°F or feverish (Days 1-14) | 12.4% | 35.7% | 10.8% | 10.3% |
| | N=243 | N=285 | N=221 | N=237 |
| Temperature ≥ 100.4°F | 10.3% | 16.8% | 10% | 4.2% |
| Temperature ≥ 102.2 °F | 2.1% | 3.5% | 2.3% | 2.5% |

^{*}Pneumococcal 7-valent Conjugate Vaccine

N=number of subjects for whom data are available.

Table 2: Incidences of Unsolicited Systemic Adverse Events ≥5% in Any Group Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly With ProQuad and PREVNAR*

| | Dose 1 | | Dose 2 | | | |
|-----------------------------------|-----------------------------|---|-------------|-------------------------------|--|--|
| Adverse Event: Days 1-14 | VAQTA alone | VAQTA + ProQuad + PREVNAR concomitantly | VAQTA alone | VAQTA + ProQuad concomitantly | | |
| | N=274 | N=311 | N=251 | N=263 | | |
| General Disorders and A | dministration Site Con | ditions | | | | |
| Irritability | 3.6% | 6.1% | 2.8% | 2.7% | | |
| Infections and Infestation | Infections and Infestations | | | | | |
| Upper respiratory tract infection | 3.3% | 6.1% | 4.8% | 5.7% | | |
| Skin and Subcutaneous | Tissue Disorders | | | | | |
| Dermatitis diaper | 1.1% | 6.1% | 2.4% | 3.4% | | |

^{*}Pneumococcal 7-valent Conjugate Vaccine

In Stage I of an open, multicenter, randomized study, children 15 months of age were randomized to receive the first dose of VAQTA alone (N=151) or concomitantly with PedvaxHIB and INFANRIX (N=155); another group of children 15 months of age were randomized to receive the first dose of VAQTA alone (N=152) or concomitantly with PedvaxHIB (N=159). All groups received the second dose of VAQTA alone at least 6 months following the first dose. The race distribution of Stage I study subjects was: 63.9% Caucasian; 17.5% Hispanic-American; 14.7% Black; 2.6% other; and 1.3% Asian. The distribution of subjects by gender was 54.0% male and 46.0% female. In Stage II of this study, an additional 654 children 12-17 months of age received the first dose of VAQTA alone followed by the second dose of VAQTA 6 months later. The race distribution of Stage II of the study subjects was: 66.1% Caucasian; 10.6% Hispanic-American; 16.8% Black; 4.7% other; and 1.5% Asian. The distribution of subjects by gender was 51.2% male and 48.8% female.

Table 3 presents rates of solicited local reactions at the VAQTA injection-site and rates of elevated temperatures (≥100.4°F and ≥102.2°F) that occurred within 5 days following each dose of VAQTA and elevated temperatures >98.6°F for a total of 14 days following each dose of VAQTA. Occurrences of these events were recorded daily on diary cards. Table 4 presents rates of unsolicited systemic adverse events that occurred within 14 days at ≥5% following each dose of VAQTA.

Table 3: Incidences of Solicited Local Adverse Reactions at the VAQTA Injection Site and Elevated Temperatures
Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly with
PedvaxHIB With or Without INFANRIX (Stage I) and those Receiving VAQTA Alone at Both Doses (Stage II)

| | Stage I | | | Sta | age II |
|---|-------------|---|-------------|-------------|-------------|
| | Dose 1 | | Dose 2 | Dose 1 | Dose 2 |
| Adverse Reaction: Days 1-5 unless noted | VAQTA alone | VAQTA + PedvaxHIB and Infanrix or VAQTA + PedvaxHIB concomitantly | VAQTA alone | VAQTA alone | VAQTA alone |
| Injection site adverse reactions | N=256 | N=302 | N=503 | N=647 | N=599 |
| Injection site erythema | 18.0% | 19.9% | 21.5% | 11.7% | 16.2% |
| Injection site pain/tenderness | 21.9% | 36.4% | 27.4% | 20.1% | 22.9% |
| Injection site swelling | 10.2% | 14.2% | 10.1% | 7.1% | 7.0% |
| Temperature > 98.6°F or feverish (Days 1- 14) | 10.2% | 17.2% | 10.7% | 10.0% | 8.2% |
| | N=234 | N=290 | N=473 | N=631 | N=591 |
| Temperature ≥ 100.4°F | 9.0% | 16.9% | 9.1% | 9.4% | 8.6% |
| Temperature ≥ 102.2 °F | 3.8% | 3.1% | 3.2% | 2.9% | 2.4% |

N= number of subjects for whom data is available

Table 4: Incidences of Unsolicited Systemic Adverse Events ≥5% in Any Group Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly with PedvaxHIB With or Without INFANRIX (Stage I) and Those Receiving VAQTA Alone at Both Doses (Stage II)

| | Stage I | | | Sta | ge II |
|-----------------------------------|-----------------------|---|-------------|-------------|-------------|
| | Do | se 1 | Dose 2 | Dose 1 | Dose 2 |
| Adverse Event: Days 1-14 | VAQTA alone | VAQTA + PedvaxHIB and Infanrix or VAQTA + PedvaxHIB concomitantly | VAQTA alone | VAQTA alone | VAQTA alone |
| | N=256 | N=302 | N=503 | N=647 | N=599 |
| Gastrointestinal Disord | ers | | | | |
| Diarrhea | 3.9% | 8.3% | 3.8% | 4.6% | 3.8% |
| Teething | 3.1% | 2.3% | 1.4% | 5.7% | 4.3% |
| General Disorders and | Administration Site (| Conditions | | | |
| Irritability | 6.3% | 9.6% | 4.0% | 8.8% | 6.5% |
| Infections and Infestation | ons | | | | |
| Upper respiratory tract infection | 2.3% | 3.3% | 3.0% | 4.9% | 5.2% |
| Respiratory, Thoracic a | nd Mediastinal Disor | ders | | | |
| Rhinorrhea | 2.0% | 4.0% | 3.8% | 6.2% | 3.8% |

Data presented in Tables 1 through 4 on solicited local reactions, and solicited and unsolicited systemic adverse events with incidence ≥5% following each dose of VAQTA are representative of other clinical trials of VAQTA in children 12 through 23 months of age. Across the five studies conducted in children 12-23 months of age, ≥39.9% of subjects experienced local adverse reactions and ≥55.7% of subjects experienced systemic adverse events. The majority of local and systemic adverse events were mild to moderate in intensity.

The following additional unsolicited local adverse reactions and systemic adverse events were observed at a common frequency of ≥1% to <10% in any individual clinical study. This listing includes only the

adverse reactions not reported elsewhere in the label. These local adverse reactions and systemic adverse events occurred among recipients of VAQTA alone or VAQTA given concomitantly within 14 days following any dose of VAQTA across four clinical studies.

Eye disorders: Conjunctivitis

Gastrointestinal disorders: Constipation; vomiting

General disorders and administration site conditions: Injection-site bruising; injection-site ecchymosis

Infections and infestations: Otitis media; nasopharyngitis; rhinitis; viral infection; croup; pharyngitis streptococcal; laryngotracheobronchitis; viral exanthema; gastroenteritis viral; roseola

Metabolism and nutrition disorders: Anorexia

Psychiatric disorders: Insomnia; crying

Respiratory, thoracic and mediastinal disorders: Cough; nasal congestion; respiratory congestion

Skin and subcutaneous tissue disorders: Rash vesicular; measles-like/rubella-like rash; varicella-like rash; rash morbilliform

Serious Adverse Events (Children 12 through 23 Months of Age): Across the five studies conducted in subjects 12-23 months of age, 0.7% (32/4374) of subjects reported a serious adverse event following any dose of VAQTA, and 0.1% (5/4374) of subjects reported a serious adverse event judged to be vaccine related by the study investigator. The serious adverse events were collected over the period defined in each protocol (14, 28, or 42 days). Vaccine-related serious adverse events which occurred following any dose of VAQTA with or without concomitant vaccines included febrile seizure (0.05%), dehydration (0.02%), gastroenteritis (0.02%), and cellulitis (0.02%).

Children/Adolescents — 2 Years through 18 Years of Age

In 11 clinical trials, 2615 healthy children 2 years through 18 years of age received at least one dose of VAQTA. These studies included administration of VAQTA in varying doses and regimens (1377 children received one or more 25U doses). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 84.7% Caucasian; 10.6% American Indian; 2.3% African-American; 1.5% Hispanic-American; 0.6% other; 0.2% Oriental. The distribution of subjects by gender was 51.2% male and 48.8% female.

In a double-blind, placebo-controlled efficacy trial (i.e. The Monroe Efficacy Study), 1037 healthy children and adolescents 2 through 16 years of age were randomized to receive a primary dose of 25U of VAQTA and a booster dose of VAQTA 6, 12, or 18 months later, or placebo (alum diluent). All study subjects were Caucasian: 51.5% were male and 48.5% were female. Subjects were followed days 1 to 5 postvaccination for fever and local adverse reactions and days 1 to 14 for systemic adverse events. The most common adverse events/reactions were injection-site reactions, reported by 6.4% of subjects. Table 5 summarizes local adverse reactions and systemic adverse events reported in ≥1% of subjects. There were no significant differences in the rates of any adverse events or adverse reactions between vaccine and placebo recipients after Dose 1.

Table 5: Local Adverse Reactions and Systemic Adverse Events (≥1%) in Healthy Children and Adolescents from the Monroe Efficacy Study

| | | QTA | Diacoba / Alum | |
|-----------------------|---------------------------|---------------------------|---|--|
| Adverse Event | | 519) | Placebo (Alum Diluent)* ^{†,‡} | |
| | Dose 1* Rate (Percent) | Booster Rate (Percent) | (N=518) Rate (Percent) | |
| Injection Site§ | n=515 | n=475 | n=510 | |
| Pain | 6.4% | 3.4% | 6.3% | |
| Tenderness | 4.9% | 1.7% | 6.1% | |
| Erythema | 1.9% | 0.8% | 1.8% | |
| Swelling | 1.7% | 1.5% | 1.6% | |
| Warmth | 1.7% | 0.6% | 1.6% | |
| Systemic [¶] | n=519 | n=475 | n=518 | |
| Abdominal pain | 1.2% | 1.1% | 1.0% | |
| Pharyngitis | 1.2% | 0% | 0.8% | |
| Headache | 0.4% | 0.8% | 1.0% | |

N=Number of subjects enrolled/randomized.

Percent=percentage of subjects for whom data are available with adverse event n=number of subjects for whom adverse events available

Adults — 19 Years of Age and Older

In an open-label clinical trial, 240 healthy adults 18 to 54 years of age were randomized to receive either VAQTA (50U/1-mL) with Typhim Vi (Typhoid Vi polysaccharide vaccine) and YF-Vax (yellow fever vaccine) concomitantly (N=80), typhoid Vi polysaccharide and yellow fever vaccines concomitantly (N=80), or VAQTA alone (N=80). Approximately 6 months later, subjects who received VAQTA were administered a second dose of VAQTA. The race distribution of the study subjects who received VAQTA with or without typhoid Vi polysaccharide and yellow fever vaccine was as follows: 78.3% Caucasian; 14.2% Oriental; 3.3% other; 2.1% African-American; 1.7% Indian; 0.4% Hispanic-American. The distribution of subjects by gender was 40.8% male and 59.2% female. Subjects were monitored for local adverse reactions and fever for 5 days and systemic adverse events for 14 days after each vaccination. In the 14 days after the first dose of VAQTA, the proportion of subjects with adverse events was similar between recipients of VAQTA given concomitantly with typhoid Vi polysaccharide and yellow fever vaccines compared to recipients of typhoid Vi polysaccharide and yellow fever vaccines without VAQTA. Table 6 summarizes solicited local adverse reactions and Table 7 summarizes unsolicited systemic adverse events reported in ≥5% in adults who received one or two doses of VAQTA alone and for subjects who received VAQTA concomitantly with typhoid Vi polysaccharide and yellow fever vaccines. There were no solicited systemic complaints reported at a rate ≥5%. Fever ≥101°F occurred in 1.3% of subjects in each group.

Table 6: Incidences of Solicited Local Adverse Reactions in Healthy Adults ≥19 Years of Age Occurring at ≥5% After Any Dose

| Adverse Event | VAQTA administered alone (N=80) | VAQTA + ViCPS* and Yellow Fever vaccines administered concomitantly [†] (N=80) | | |
|-----------------------------|---------------------------------------|--|--|--|
| | Rate (Percent) | | | |
| Injection-site [‡] | | | | |
| | | | | |
| Pain/tenderness/soreness | 78.8% | 70.3% | | |
| | 78.8% 23.7% | 70.3% 23.7% | | |
| Pain/tenderness/soreness | | | | |

N=Number of subjects enrolled/randomized.

^{*} No statistically significant differences between the two groups.

[†] Second injection of placebo not administered because code for the trial was broken.

[‡] Placebo (Álum diluent) = amorphous aluminum hydroxyphosphate sulfate.

[§] Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination with VAQTA

[¶] Systemic adverse events reported Days 1-15 after vaccination, regardless of causality.

Percent=percentage of subjects with adverse event.

*ViCPS=Typhoid Vi polysaccharide vaccine.

[†]VAQTA administered concomitantly with typhoid Vi polysaccharide (ViCPS) and yellow fever vaccines.

[‡] Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination

Table 7: Incidences of Unsolicited Systemic Adverse Events in Adults ≥19 Years of Age Occurring at ≥5% After Any Dose

| Body System Adverse Event | VAQTA administered alone (N=80) | VAQTA + ViCPS* and Yellow Fever vaccines administered concomitantly [†] (N=80) | | | |
|-----------------------------|--|--|--|--|--|
| | Rate (Percent) | | | | |
| General disorders and a | | | | | |
| Asthenia/fatigue | 7.5% | 11.3% | | | |
| Chills | 1.3% | 7.5% | | | |
| Gastrointestinal disorde | rs [‡] | | | | |
| Nausea | 7.5% | 12.5% | | | |
| Musculoskeletal and cor | nnective tissue disorders | . ‡ | | | |
| Myalgia | 5.0% | 10.0% | | | |
| Arm pain | 0.0% | 6.3% | | | |
| Nervous system disorde | rs [‡] | | | | |
| Headache | 23.8% | 26.3% | | | |
| Infections and infestation | Infections and infestations [‡] | | | | |
| Upper respiratory infection | 7.5% | 3.8% | | | |
| Pharyngitis | 2.5% | 6.3% | | | |

N=Number of subjects enrolled/randomized with data available.

In four clinical trials involving 1645 healthy adults 19 years of age and older who received one or more 50U doses of hepatitis A vaccine, subjects were followed for fever and local adverse reactions 1 to 5 days postvaccination and for systemic adverse events 1 to 14 days postvaccination. One single-blind study evaluated doses of VAQTA with varying amounts of viral antigen and/or alum content in healthy adults ≥170 pounds and ≥30 years of age (N=210 adults administered 50U/1-mL dose). One open-label study evaluated VAQTA given with immune globulin (IG) or alone (N=164 adults who received VAQTA alone). A third study was single-blind and evaluated 3 different lots of VAQTA (N=1112). The fourth study that was also single-blind evaluated doses of VAQTA with varying amounts of viral antigen in healthy adults ≥170 pounds and ≥30 years of age (N=159 adults administered the 50U/1-mL dose). Overall, the race distribution of the study subjects who received at least one dose of VAQTA was as follows: 94.2% Caucasian; 2.2% Black; 1.5% Hispanic; 1.5% Oriental; 0.4% other; 0.2% American Indian. 47.6% of subjects were male and 52.4% were female. The most common adverse event/reaction was injection-site pain/soreness/tenderness reported by 67.0% of subjects. Of all reported injection-site reactions 99.8% were mild (i.e., easily tolerated with no medical intervention) or moderate (i.e., minimally interfered with usual activity possibly requiring little medical intervention). Listed below in Table 8 are the local adverse reactions and systemic adverse events reported by ≥5% of subjects, in decreasing order of frequency within each body system.

Table 8: Incidences of Local Adverse Reactions and Systemic Adverse Events ≥5% in Adults 19 Years of Age and Older

| Body System | VAQTA (Any Dose) (N=1645) |
|--|------------------------------|
| Adverse Events | Rate (n/total n) |
| Nervous system disorders* | n=1641 |
| Headache | 16.1% |
| General disorders and administration site reactions [†] | n=1640 |
| Injection-site | 67.0% |

Percent=percentage of subjects with adverse event for whom data are available.

^{*}ViCPS=Typhoid Vi polysaccharide vaccine.

[†]VAQTA administered concomitantly with typhoid Vi polysaccharide (ViCPS) and yellow fever vaccines.

[‡]Systemic Adverse Events reported Days 1-15 after vaccination, regardless of causality.

| pain/tenderness/soreness | |
|--------------------------|-------|
| Injection-site warmth | 18.2% |
| Injection-site swelling | 14.7% |
| Injection-site erythema | 13.7% |

N=Number of subjects enrolled/randomized.

The following additional unsolicited systemic adverse events were observed among recipients of VAQTA that occurred within 14 days at a common frequency of ≥1% to <10% following any dose not reported elsewhere in the label. These adverse reactions have been reported across 4 clinical studies.

Musculoskeletal and connective tissue disorders: Back pain; stiffness

Reproductive system and breast disorders: Menstruation disorders

6.2 Post-Marketing Experience

The following additional adverse events have been reported with use of the marketed vaccine. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to a vaccine exposure.

Blood and lymphatic disorders: Thrombocytopenia.

Nervous system disorders: Guillain-Barré syndrome; cerebellar ataxia; encephalitis.

Post-Marketing Observational Safety Study

In a post-marketing, 60-day safety surveillance study, conducted at a large health maintenance organization in the United States, a total of 42,110 individuals ≥2 years of age received 1 or 2 doses of VAQTA (13,735 children/adolescents and 28,375 adult subjects). Safety was passively monitored by electronic search of the automated medical records database for emergency room and outpatient visits, hospitalizations, and deaths. Medical charts were reviewed when an event was considered to be possibly vaccine-related by the investigator. None of the serious adverse events identified were assessed as being related to vaccine by the investigator. Diarrhea/gastroenteritis, resulting in outpatient visits, was determined by the investigator to be the only vaccine-related nonserious adverse reaction in the study. There was no vaccine-related adverse reaction identified that had not been reported in earlier clinical trials with VAQTA.

7 DRUG INTERACTIONS

7.1 Use with Other Vaccines

Do not mix VAQTA with any other vaccine in the same syringe or vial. Use separate injection sites and syringes for each vaccine. Please refer to package inserts of coadministered vaccines.

In clinical trials in children, VAQTA was concomitantly administered with one or more of the following US licensed vaccines: Measles, Mumps, and Rubella Virus Vaccine, Live; Varicella Vaccine, Live; Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed; Measles, Mumps, Rubella, and Varicella Vaccine, Live; Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇); and Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate). Safety and immunogenicity were similar for concomitantly administered vaccines compared to separately administered vaccines.

In clinical trials in adults, VAQTA was concomitantly administered with typhoid Vi polysaccharide and yellow fever vaccines [see Adverse Reactions (6.1) and Clinical Studies (14.2, 14.7)]. Safety and immunogenicity were similar for concomitantly administered vaccines compared to separately administered vaccines.

n=Number of subjects in each category with data available.

Percent=percentage of subjects for whom data are available with adverse event.

^{*}Systemic Adverse Events reported Days 1 to 14 after vaccination, regardless of causality.

[†]Adverse Reactions at the injection site (VAQTA) and measured fever Days 1 to 5 after vaccination.

7.2 Use with Immune Globulin

VAQTA may be administered concomitantly with Immune Globulin, human, using separate sites and syringes. The recommended vaccination regimen for VAQTA should be followed. Consult the manufacturer's product circular for the appropriate dosage of Immune Globulin. A booster dose of VAQTA should be administered at the appropriate time as outlined in the recommended regimen for VAQTA [see Clinical Studies (14.5)].

7.3 Immunosuppressive Therapy

If VAQTA is administered to a person receiving immunosuppressive therapy, an adequate immunologic response may not be obtained.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are no adequate and well-controlled studies designed to evaluate VAQTA in pregnant women. Available post-approval data do not suggest an increased risk of miscarriage or major birth defects in women who received VAQTA during pregnancy.

Developmental toxicity studies have not been conducted with VAQTA in animals.

Data

Human Data

Post-approval adverse reactions are reported voluntarily from a population of uncertain size. It is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

In prospectively reported spontaneous post-approval reports from 1995 to 2018, 36 women with a known pregnancy outcome were exposed to VAQTA during pregnancy following the last menstrual period. After excluding induced abortions (n=4) and those with exposure in the third trimester (n=2), there were 30 pregnancies with known outcomes with exposures in the first or second trimester. Miscarriage was reported for 3 of 30 (10%) pregnancies. Major birth defects were reported for 1 of 27 (3.7%) live born infants. The rates of miscarriage and major birth defects were consistent with estimated background rates.

8.2 Lactation

Risk Summary

It is not known whether VAQTA is excreted in human milk. Data are not available to assess the effects of VAQTA on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VAQTA and any potential adverse effects on the breastfed child from VAQTA or from the underlying maternal condition. For preventive vaccines the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety of VAQTA has been evaluated in 4374 children 12 through 23 months of age, and 2615 children/adolescents 2 through 18 years of age who received at least one 25U dose of VAQTA [see Adverse Reactions (6) and Dosage and Administration (2)].

Safety and effectiveness in infants below 12 months of age have not been established.

8.5 Geriatric Use

In the post-marketing observational safety study which included 42,110 persons who received VAQTA [see Adverse Reactions (6.2)], 4769 persons were 65 years of age or older and 1073 persons were 75 years of age or older. There were no adverse events judged by the investigator to be vaccine-related in the geriatric study population. In other clinical studies, 68 subjects 65 years of age or older were vaccinated with VAQTA, 10 of whom were 75 years of age or older. No overall differences in safety and immunogenicity were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Immunocompromised Individuals

Immunocompromised persons may have a diminished immune response to VAQTA and may not be protected against HAV infection.

11 DESCRIPTION

VAQTA is an inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. The virus is grown, harvested, purified by a combination of physical and high performance liquid chromatographic techniques developed at the Merck Research Laboratories, formalin inactivated, and then adsorbed onto amorphous aluminum hydroxyphosphate sulfate.

VAQTA is a sterile suspension for intramuscular injection. One milliliter of the vaccine contains approximately 50U of hepatitis A virus antigen, which is purified and formulated without a preservative. Within the limits of current assay variability, the 50U dose of VAQTA contains less than 0.1 mcg of non-viral protein, less than 4×10^{-6} mcg of DNA, less than 10^{-4} mcg of bovine albumin, and less than 0.8 mcg of formaldehyde. Other process chemical residuals are less than 10 parts per billion (ppb), including neomycin.

Each 0.5-mL pediatric dose contains 25U of hepatitis A virus antigen and adsorbed onto approximately 0.225 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 35 mcg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

Each 1-mL adult dose contains 50U of hepatitis A virus antigen and adsorbed onto approximately 0.45 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 70 mcg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VAQTA has been shown to elicit antibodies to hepatitis A as measured by ELISA.

Protection from hepatitis A disease has been shown to be related to the presence of antibody. However, the lowest titer needed to confer protection has not been determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VAQTA has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility. [See Use in Specific Populations (8).]

14 CLINICAL STUDIES

14.1 Efficacy of VAQTA: The Monroe Clinical Study

The immunogenicity and protective efficacy of VAQTA were evaluated in a randomized, double-blind, placebo-controlled study involving 1037 susceptible healthy children and adolescents 2 through 16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (The Monroe Efficacy Study). All of these children were Caucasian, and there were 51.5% male and 48.5% female. Each child received an intramuscular dose of VAQTA (25U) (N=519) or placebo (alum diluent) (N=518). Among those individuals who were initially seronegative (measured by a modification of the HAVAB radioimmunoassay [RIA]),

seroconversion was achieved in >99% of vaccine recipients within 4 weeks after vaccination. The onset of seroconversion following a single dose of VAQTA was shown to parallel the onset of protection against clinical hepatitis A disease.

Because of the long incubation period of the disease (approximately 20 to 50 days, or longer in children), clinical efficacy was based on confirmed cases 1 of hepatitis A occurring ≥ 50 days after vaccination in order to exclude any children incubating the infection before vaccination. In subjects who were initially seronegative, the protective efficacy of a single dose of VAQTA was observed to be 100% with 21 cases of clinically confirmed hepatitis A occurring in the placebo group and none in the vaccine group (p<0.001). The number of clinically confirmed cases of hepatitis A ≥ 30 days after vaccination were also compared. In this analysis, 28 cases of clinically confirmed hepatitis A occurred in the placebo group while none occurred in the vaccine group ≥ 30 days after vaccination. In addition, it was observed in this trial that no cases of clinically confirmed hepatitis A occurred in the vaccine group after day 16.2 Following demonstration of protection with a single dose and termination of the study, a booster dose was administered to a subset of vaccinees 6, 12, or 18 months after the primary dose.

No cases of clinically confirmed hepatitis A disease ≥50 days after vaccination have occurred in those vaccinees from The Monroe Efficacy Study monitored for up to 9 years.

14.2 Other Clinical Studies

The efficacy of VAQTA in other age groups was based upon immunogenicity measured 4 to 6 weeks following vaccination. VAQTA was found to be immunogenic in all age groups.

Children — 12 through 23 Months of Age

In a clinical trial, children 12 through 23 months of age were randomized to receive the first dose of VAQTA with or without M-M-R II and VARIVAX (N=617) and the second dose of VAQTA with or without Tripedia and optionally either oral poliovirus vaccine (no longer licensed in the US) or IPOL (N=555). The race distribution of study subjects who received at least one dose of VAQTA was as follows: 56.7% Caucasian; 17.5% Hispanic-American; 14.3% African-American; 7.0% Native American; 3.4% other; 0.8% Oriental; 0.2% Asian; and 0.2% Indian. The distribution of subjects by gender was 53.6% male and 46.4% female. In the analysis population, there were 471 initially seronegative children 12 through 23 months of age, who received the first dose of VAQTA with (N=237) or without (N=234) M-M-R II and VARIVAX of whom 96% (95% CI: 93.7%, 97.5%) seroconverted (defined as having an anti-HAV titer ≥10 mIU/mL) post dose 1 with an anti-HAV geometric mean titer (GMT) of 48 mIU/mL (95% CI: 44.7, 51.6). There were 343 children in the analysis population who received the second dose of VAQTA with (N=168) or without (N=175) Tripedia and optional oral poliovirus vaccine or IPOL of whom 100% (95% CI: 99.3%, 100%) seroconverted post dose 2 with an anti-HAV GMT of 6920 mIU/mL (95% CI: 6136, 7801). Of children who received only VAQTA at both visits, 100% (n=97) seroconverted after the second dose of VAQTA.

In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly, and 323 were randomized to receive ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later. The race distribution of the study subjects was as follows: 60.3% Caucasian; 21.6% African-American; 9.5% Hispanic-American; 7.2% other; 1.1% Asian/Pacific; and 0.3% Native American. The distribution of subjects by gender was 50.7% male and 49.3% female. In the analysis population, the seropositivity rate for hepatitis A antibody (defined as the percent of subjects with an anti-HAV titer ≥10 mIU/mL) was 100% (n=182; 95% CI: 98.0%, 100%) post dose 2 with an anti-HAV GMT of 4977 mIU/mL (95% CI: 4068, 6089) when VAQTA was given with ProQuad and pneumococcal 7-valent conjugate vaccine and 99.4% (n=159, 95% CI: 96.5%, 100%) post dose 2 with an anti-HAV GMT of 6123 mIU/mL (95% CI: 4826, 7770) when VAQTA alone was given. These seropositivity rates were similar

¹The clinical case definition included all of the following occurring at the same time: 1) one or more typical clinical signs or symptoms of hepatitis A (e.g., jaundice, malaise, fever ≥38.3°C); 2) elevation of hepatitis A IgM antibody (HAVAB-M); 3) elevation of alanine transferase (ALT) ≥2 times the upper limit of normal.

²One vaccinee did not meet the pre-defined criteria for clinically confirmed hepatitis A but did have positive hepatitis A IgM and borderline liver enzyme (ALT) elevations on days 34, 50, and 58 after vaccination with mild clinical symptoms observed on days 49 and 50.

whether VAQTA was administered with or without ProQuad and pneumococcal 7-valent conjugate vaccine.

In an open, multicenter, randomized study involving 617 children 15 months of age, 306 were randomized to receive VAQTA with or without PedvaxHIB and INFANRIX, and 311 were randomized to receive VAQTA with or without PedvaxHIB. The race distribution of the study subjects was as follows: 63.9% Caucasian; 17.5% Hispanic-American; 14.7% Black; 2.6% other; and 1.3% Asian. The distribution of subjects by gender was 54.0% male and 46.0% female. The seropositivity rate for hepatitis A antibody (defined as the percent of subjects with an anti-HAV titer ≥ 10 mIU/mL) 4 weeks post dose 2 was 100% (n=208, 95% CI: 98.2%, 100.0%) in those who received VAQTA concomitantly with PedvaxHIB and INFANRIX or concomitantly with PedvaxHIB. In those subjects who received VAQTA alone, the seropositivity rate for hepatitis A antibody was 100% (n=183, 95% CI: 98.0%, 100.0%), regardless of baseline hepatitis A serostatus. Overall, the anti-HAV GMT in the concomitant groups was 3616.5 mIU/mL (95% CI: 3084.5, 4240.2). The anti-HAV GMT in the nonconcomitant groups was 4712.6 mIU/mL (95% CI: 3996.8, 5556.8). Comparable responses were observed in both the initially seronegative and seropositive subjects.

In three combined clinical studies 1022 initially seronegative subjects received 2 doses of VAQTA alone or concomitantly with other vaccines. Of the seronegative subjects, 99.9% achieved an anti-HAV titer ≥10 mIU/mL (95% CI: 99.5%, 100%) and an anti-HAV GMT of 5392.1 mIU/mL (95% CI: 4996.5, 5819.0) 4 weeks following dose 2 of VAQTA.

Children/Adolescents — 2 Years through 18 Years of Age

Immunogenicity data were combined from eleven randomized clinical studies in children and adolescents 2 through 18 years of age who received VAQTA (25U/0.5 mL). These included administration of VAQTA in varying doses and regimens (N=404 received 25U/0.5 mL), the Monroe Efficacy Study (N=973), and comparison studies for process and formulation changes (N=1238). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 84.8% Caucasian; 10.6% American Indian; 2.3% African-American; 1.5% Hispanic-American; 0.6% other; 0.2% Oriental. The distribution of subjects by gender was 51.2% male and 48.8% female. The proportions of subjects who seroconverted 4 weeks after the first and second doses administered 6 months apart were 97% (n=1230; 95% CI: 96%, 98%) and 100% (n=1057; 95% CI: 99.5%, 100%) of subjects with anti-HAV GMTs of 43 mIU/mL (95% CI: 40, 45) and 10,077 mIU/mL (95% CI: 9394, 10,810), respectively.

Adults — 19 Years of Age and Older

Immunogenicity data were combined from five randomized clinical studies in adults 19 years of age and older who received VAQTA (50U/1-mL). One single-blind study evaluated doses of VAQTA with varying amounts of viral antigen and/or alum content in healthy adults ≥170 pounds and ≥30 years of age (N=208 adults administered 50U/1-mL dose). One open-label study evaluated VAQTA given with immune globulin or alone (N=164 adults who received VAQTA alone). A third study was single-blind and evaluated 3 different lots of VAQTA (N=1112). The fourth study was single-blind and evaluated doses of VAQTA with varying amounts of viral antigen in healthy adults ≥170 pounds and ≥30 years of age (N=159 adults administered the 50U/1-mL dose). The fifth study was an open-label study to evaluate various regimens for time of administration of the booster dose of VAQTA (6, 12, and 18 months post dose 1, N=354). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 93.2% Caucasian; 2.5% African-American; 2.1% Hispanic-American; 1.4% Oriental; 0.5% other; 0.3% American Indian. The distribution of subjects by gender was 44.8% male and 55.2% female. The proportion of subjects who seroconverted 4 weeks after the first and second doses administered 6 months apart was 95% (n=1411; 95% CI: 94%, 96%) and 99.9% (n=1244; 95% CI: 99.4%, 100%) with GMTs of 37 mIU/mL (95% CI: 35, 38) and 6013 mIU/mL (95% CI: 5592, 6467), respectively. Furthermore, at 2 weeks postvaccination, 69.2% (n=744; 95% CI: 65.7%, 72.5%) of adults seroconverted with an anti-HAV GMT of 16 mIU/mL after a single dose of VAQTA.

14.3 Timing of Booster Dose Administration

Children/Adolescents — 2 through 18 Years of Age

In the Monroe Efficacy Study, children were administered a second dose of VAQTA (25U/0.5 mL) 6, 12, or 18 months following the initial dose. For subjects who received both doses of VAQTA, the GMTs and

proportions of subjects who seroconverted 4 weeks after the booster dose administered 6, 12, and 18 months after the first dose are presented in Table 9.

Table 9: Children/Adolescents from the Monroe Efficacy Study
Seroconversion Rates (%) and Geometric Mean Titers (GMT) for Cohorts of Initially Seronegative Vaccinees at the Time of the Booster(25U) and 4 Weeks Later

| | the booster | (250) and 4 weeks Later | | |
|---|---|-----------------------------------|---|--|
| Months Following Initial 25U Dose | Cohort [*] (n=960) 0 and 6 Months | Cohort* (n=35) 0 and 12 Months | Cohort [*] (n=39) 0 and 18 Months | |
| | Seroconversion Rate GMT (mIU/mL) (95% CI) | | | |
| 6 | 97% 107 (98, 117) | _ | _ | |
| 7 | 100% 10433 (9681, 11243) | _ | _ | |
| 12 | _ | 91% 48 (33, 71) | _ | |
| 13 | _ | 100% 12308 (9337, 16226) | _ | |
| 18 | _ | _ | 90% 50 (28, 89) | |
| 19 | _ | _ | 100% 9591 (7613, 12082) | |

^{*}Blood samples were taken at prebooster and postbooster time points.

Adults — 19 years of age and older

Among the 5 randomized clinical studies in adults 19 years of age and older described in Section 14.2, there were additional data in which a booster dose of VAQTA (50U/1-mL) was administered 12 or 18 months after the first dose. For subjects in these studies who received both doses of VAQTA, the proportions who seroconverted 4 weeks after the booster dose administered 6, 12, and 18 months after the first dose were 100% of 1201 subjects, 98% of 91 subjects, and 100% of 84 subjects, respectively. GMTs in mIU/mL one month after the subjects received the booster dose at 6, 12, or 18 months after the primary dose were 5987 mIU/mL (95% CI: 5561, 6445), 4896 mIU/mL (95% CI: 3589, 6679), and 6043 mIU/mL (95% CI: 4687, 7793), respectively.

14.4 Duration of Immune Response

In follow-up of subjects in The Monroe Efficacy Study, in children (≥ 2 years of age) and adolescents who received two doses (25U) of VAQTA, detectable levels of anti-HAV antibodies (≥ 10 mIU/mL) were present in 100% of subjects for at least 10 years postvaccination. In subjects who received VAQTA at 0 and 6 months, the GMT was 819 mIU/mL (n=175) at 2.5 to 3.5 years and 505 mIU/mL (n=174) at 5 to 6 years, and 574 mIU/mL (n=114) at 10 years postvaccination. In subjects who received VAQTA at 0 and 12 months, the GMT was 2224 mIU/mL (n=49) at 2.5 to 3.5 years, 1191 mIU/mL (n=47) at 5 to 6 years, and 1005 mIU/mL (n=36) at 10 years postvaccination. In subjects who received VAQTA at 0 and 18 months, the GMT was 2501 mIU/mL (n=53) at 2.5 to 3.5 years, 1614 mIU/mL (n=56) at 5 to 6 years, and 1507 mIU/mL (n=41) at 10 years postvaccination.

In adults that were administered VAQTA at 0 and 6 months, the hepatitis A antibody response to date has been shown to persist at least 6 years. Detectable levels of anti-HAV antibodies (\geq 10 mIU/mL) were present in 100% (378/378) of subjects with a GMT of 1734 mIU/mL at 1 year, 99.2% (252/254) of subjects with a GMT of 687 mIU/mL at 2 to 3 years, 99.1% (219/221) of subjects with a GMT of 605 mIU/mL at 4 years, and 99.4% (170/171) of subjects with a GMT of 684 mIU/mL at 6 years postvaccination.

The total duration of the protective effect of VAQTA in healthy vaccinees is unknown at present.

14.5 Concomitant Administration of VAQTA and Immune Globulin

The concurrent use of VAQTA (50U) and immune globulin (IG, 0.06 mL/kg) was evaluated in an open-label, randomized clinical study involving 294 healthy adults 18 to 39 years of age. Adults were randomized to receive 2 doses of VAQTA 24 weeks apart (N=129), the first dose of VAQTA concomitant with a dose of IG followed by the second dose of VAQTA alone 24 weeks later (N=135), or IG alone

(N=30). The race distribution of the study subjects who received at least one dose of VAQTA or IG in this study was as follows: 92.3% Caucasian; 4.0% Hispanic-American; 3.0% African-American; 0.3% Native American; 0.3% Asian/Pacific. The distribution of subjects by gender was 28.7% male and 71.3% female. Table 10 provides seroconversion rates and GMTs at 4 and 24 weeks after the first dose in each treatment group and at one month after a booster dose of VAQTA (administered at 24 weeks) [see Drug Interactions (7.2)].

Table 10: Seroconversion Rates (%) and Geometric Mean Titers (GMT) After Vaccination with VAQTA Plus IG, VAQTA Alone, and IG Alone

| | VAQTA plus IG | VAQTA | IG | | |
|---|--|--------------------------------------|---|--|--|
| Weeks | Seroconversion Rate GMT (mIU/mL) (95% CI) | | | | |
| 4 | 100% 42 (39, 45) (n=129) | 96% 38 (33, 42) (n=135) | 87% 19 (15, 23) (n=30) | | |
| 24 | 92% 83 (65, 105) (n=125) | 97%* 137* (112, 169) (n=132) | 0% Undetectable [†] (n=28) | | |
| 100% 28 4872 (3716, 6388) (n=114) | | 100% 6498 (5111, 8261) (n=128) | N/A | | |

^{*}The seroconversion rate and the GMT in the group receiving VAQTA alone were significantly higher than in the group receiving VAQTA plus IG (p=0.05, p<0.001, respectively).

14.6 Interchangeability of the Booster Dose

A randomized, double-blind clinical study in 537 healthy adults, 18 to 83 years of age, evaluated the immune response to a booster dose of VAQTA and HAVRIX given at 6 or 12 months following an initial dose of HAVRIX. Subjects were randomized to receive VAQTA (50U) as a booster dose 6 months (N=232) or 12 months (N=124) following an initial dose of HAVRIX or HAVRIX (1440 EL. U) as a booster dose 6 months (N=118) or 12 months (N=63) following an initial dose of HAVRIX. The race distribution of the study subjects who received the booster dose of VAQTA or HAVRIX in this study was as follows: 87.2% Caucasian; 8.0% African-American; 1.9% Hispanic-American; 1.3% Oriental; 0.9% Asian; 0.4% Indian; 0.4% other. The distribution of subjects by gender was 44.9% male and 55.1% female. When VAQTA was given as a booster dose following HAVRIX, the vaccine produced an adequate immune response (see Table 11) [see Dosage and Administration (2.1)].

Table 11: Seropositivity Rate, Booster Response Rate* and Geometric Mean Titer 4 Weeks Following a Booster Dose of VAQTA or HAVRIX Administered 6 to 12 Months After First Dose of HAVRIX[†]

| First Dose | Booster Dose | Seropositivity Rate | Booster Response Rate* | Geometric Mean Titer |
|------------|--------------|---------------------|---------------------------|-------------------------|
| HAVRIX | VAQTA | 99.7% (n=313) | 86.1% (n=310) | 3272 (n=313) |
| 1440 EL.U. | 50 U | | | |
| HAVRIX | HAVRIX | 99.3% (n=151) | 80.1% (n=151) | 2423 (n=151) |
| 1440 EL.U. | 1440 EL.U. | ` , | , , | , , |

^{*}Booster Response Rate is defined as greater than or equal to a tenfold rise from prebooster to postbooster titer and postbooster titer ≥100 mIU/mL.

14.7 Immune Response to Concomitantly Administered Vaccines

Clinical Studies of VAQTA with M-M-R II, VARIVAX, and Tripedia

In the clinical trial in which children 12 months of age received the first dose of VAQTA concomitantly with M-M-R II and VARIVAX described in Section 14.2, rates of seroprotection to hepatitis A were similar between the two groups who received VAQTA with or without M-M-R II and VARIVAX. Measles, mumps, and rubella immune responses were tested in 241 subjects, 263 subjects, and 270 subjects, respectively. Seropositivity rates were 98.8% [95% CI: 96.4%, 99.7%] for measles, 99.6% [95% CI: 97.9%, 100%] for mumps, and 100% [95% CI: 98.6%, 100%] for rubella, which were similar to observed historical rates (seropositivity rates 99% for all three antigens, with lower bound of the 95% CI >89%) following

[†]Undetectable is defined as <10mIU/mL.

N/A = Not Applicable.

[†]Study conducted in adults 18 years of age and older.

vaccination with a first dose of M-M-R II in this age group. Data from this study were insufficient to adequately assess the immune response to VARIVAX administered concomitantly with VAQTA. In this same study, the second dose of VAQTA at 18 months of age was given with or without Tripedia (DTaP). Seropositivity rates for diphtheria and tetanus were similar to those in historical controls. However, data from this study were insufficient to assess the pertussis response of DTaP when administered with VAQTA. Rates of seroprotection to hepatitis A were similar between the two groups who received VAQTA with or without M-M-R II and VARIVAX, and between the two groups who received VAQTA with or without DTaP.

Clinical Studies of VAQTA with ProQuad and Prevnar

In the clinical trial of concomitant use of VAQTA with ProQuad and pneumococcal 7-valent conjugate vaccine in children 12 to 15 months of age described in Section 14.2, the antibody GMTs for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad and VAQTA were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent conjugate vaccine with ProQuad alone (the lower bounds of the 95% CI around the fold-difference for the 7 serotypes excluded 0.5). For the varicella component of ProQuad, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥5 gpELISA units/mL 6 weeks after their first dose of ProQuad was non-inferior (defined as -10 percentage point change) when ProQuad was administered with VAQTA and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥5 gpELISA units/mL when ProQuad was administered with pneumococcal 7-valent conjugate vaccine alone (difference in seroprotection rate -5.1% [95% CI: -9.3, -1.4%]). Hepatitis A responses were similar when compared between the two groups who received VAQTA with or without ProQuad and pneumococcal 7-valent conjugate vaccine. Seroconversion rates and antibody titers for varicella and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were similar between groups at 6 weeks postvaccination.

Clinical Studies of VAQTA with INFANRIX and PedvaxHIB

In the clinical trial of concomitant administration of VAQTA with INFANRIX and PedvaxHIB in children 15 months of age, described in Section 14.2, when the first dose of VAQTA was administered concomitantly with either INFANRIX and PedvaxHIB or PedvaxHIB, there was no interference in immune response to hepatitis A as measured by seropositivity rates after dose 2 of VAQTA compared to administration of both doses of VAQTA alone. When dose 1 of VAQTA was administered concomitantly with either PedvaxHIB and INFANRIX or PedvaxHIB, there was no interference in immune response to *Haemophilus influenzae b* (as measured by the proportion of subjects who attained an anti-polyribosylribitol phosphate antibody titer >1.0 mcg/mL at 4 weeks after vaccination), compared to subjects receiving either PedvaxHIB and INFANRIX or PedvaxHIB. When VAQTA was administered concomitantly with INFANRIX and PedvaxHIB, there was no interference in immune responses at 4 weeks after vaccination to the pertussis antigens (PT, FHA, or pertactin, as measured by GMTs) and no interference in immune responses to diphtheria toxoid or tetanus toxoid (as measured by the proportion of subjects achieving an antibody titer >0.1 IU/mL) compared to administration of INFANRIX and PedvaxHIB.

Clinical Studies of VAQTA with Typhoid Vi Polysaccharide Vaccine and Yellow Fever Vaccine, Live Attenuated

In the clinical trial of concomitant use of VAQTA with typhoid Vi polysaccharide and yellow fever vaccines in adults 18-54 years of age described in Section 6.1, the antibody response rates for typhoid Vi polysaccharide and yellow fever were adequate when typhoid Vi polysaccharide and yellow fever vaccines were administered concomitantly with (N=80) and nonconcomitantly without VAQTA (N=80). The seropositivity rate for hepatitis A when VAQTA, typhoid Vi polysaccharide, and yellow fever vaccines were administered concomitantly was generally similar to when VAQTA was given alone [see Drug Interactions (7.1)].

Data are insufficient to assess the immune response to VAQTA and poliovirus vaccine when administered concomitantly.

16 HOW SUPPLIED/STORAGE AND HANDLING

VAQTA is available in single-dose vials and prefilled Luer-Lok® syringes.

Pediatric/Adolescent Formulations

25U/0.5 mL in single-dose vials and prefilled Luer-Lok® syringes.

NDC 0006-4831-41 – box of ten 0.5-mL single dose vials.

NDC 0006-4095-02 – carton of ten 0.5-mL prefilled single-dose Luer-Lok® syringes with tip caps.

Adult Formulations

50U/1-mL in single-dose vials and prefilled Luer-Lok® syringes.

NDC 0006-4841-00 – 1-mL single dose vial.

NDC 0006-4841-41 – box of ten 1-mL single dose vials.

NDC 0006-4096-02 – carton of ten 1-mL prefilled single-dose Luer-Lok® syringes with tip caps.

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE since freezing destroys potency.

17 PATIENT COUNSELING INFORMATION

Information for Vaccine Recipients and Parents or Guardians

- Inform the patient, parent or guardian of the potential benefits and risks of the vaccine.
- Question the vaccine recipient, parent, or guardian about the occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of hepatitis A vaccine.
- Inform the patient, parent, or guardian about the potential for adverse events that have been temporally associated with administration of VAQTA.
- Tell the patient, parent, or guardian accompanying the recipient, to report adverse events to the physician or clinic where the vaccine was administered.
- Prior to vaccination, give the patient, parent, or guardian the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Tell the patient, parent, or guardian that the United States Department of Health and Human Services
 has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of
 suspected adverse events after the administration of any vaccine, including but not limited to the
 reporting of events required by the National Childhood Vaccine Injury Act of 1986. The VAERS tollfree number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at
 (www.vaers.hhs.gov).

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A CONTROLLED TRIAL OF A FORMALIN-INACTIVATED HEPATITIS A VACCINE IN HEALTHY CHILDREN

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Abstract *Background*. Although inactivated hepatitis A vaccine is known to be well tolerated and immunogenic in healthy children and adults, its efficacy has yet to be established.

Methods. To evaluate the efficacy of the hepatitis A vaccine in protecting against clinically apparent disease, we conducted a double-blind, placebo-controlled trial in a Hasidic Jewish community in upstate New York that has had recurrent outbreaks of hepatitis A. At the beginning of a summer outbreak, 1037 healthy seronegative children 2 to 16 years of age were randomly assigned to receive one intramuscular injection of a highly purified, formalininactivated hepatitis A vaccine or placebo. A case was defined by the presence of typical signs and symptoms, a diagnostic increase in IgM antibody to hepatitis A, and a serum concentration of alanine aminotransferase at least twice the upper limit of normal. Cases occurring

HEPATITIS A is a disease with a worldwide distribution; although rarely fatal, it is a common cause of morbidity in developed and developing nations. The annual cost of cases of hepatitis A in the United States is estimated to be over \$200 million. Groups at high risk include travelers, military personnel, Native Americans, children in day-care centers and their contacts, institutionalized persons, consumers of raw shellfish, and persons whose sexual practices place them at high risk.

Passive acquisition of antibodies against hepatitis A by injection of immune globulin affords protection against the clinical disease² but for only four to six months, necessitating the inconvenience, discomfort, and expense of repeated injections to ensure continuous protection. Since this is rarely practicable, particularly in high-risk groups, a vaccine capable of inducing long-lasting protection is desirable.

Titers of circulating antibodies against hepatitis A produced by immune globulin (measured either by neutralization assay³ or radioimmunoassay) are low, and within three months — well within the period of protection — they become undetectable or barely detectable.⁴ Thus, a vaccine that rapidly induces even low titers of hepatitis A antibody might be protective.

Since 1978, several hepatitis A vaccines have been prepared, some of which have been shown to be immunogenic in marmosets, chimpanzees, and hu-

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≥50 days after the injection were included in the evaluation of efficacy. The children were followed for a mean of 103 days.

Results. A total of 519 children received vaccine, and 518 received placebo. The vaccine was well tolerated, with no serious adverse reactions. From day 50 after the injection, 25 cases of clinically apparent hepatitis A occurred in the placebo group and none in the vaccine group (P<0.001), confirming that the vaccine had 100 percent protective efficacy. Before day 21, seven cases occurred in the vaccine group and three cases in the placebo group. After that time, there were no cases among vaccine recipients and 34 cases among placebo recipients.

Conclusions. The inactivated purified hepatitis A vaccine that we tested is well tolerated, and a single dose is highly protective against clinically apparent hepatitis A. (N Engl J Med 1992;327:453-7.)

mans.⁵⁻¹² The isolation, growth, and serial passage of hepatitis A virus in cell culture by Provost and Hilleman⁶ in 1979 led to the development of a live attenuated vaccine and also a prototype, formalin-inactivated vaccine derived from virus propagated in cell culture, which proved to be immunogenic and efficacious in marmosets.⁹ A single dose of live attenuated variant F' vaccine, derived from strain CR326F of the hepatitis A virus, was found to be well tolerated and immunogenic in healthy adults.¹¹ Further passage and adaptation of this F' variant in MRC-5 cell cultures produced seed virus used to manufacture the current preparation of inactivated hepatitis A vaccine.¹²

Both three-dose regimens (reinjection after one or two months and after six months) and two-dose regimens (reinjection after six months) of the inactivated vaccine have been evaluated in healthy adults and children.^{4,13-16} The vaccine has been shown to be well tolerated and immunogenic, and a single dose induces high titers of antibodies within two to four weeks.^{4,13} Geometric-mean antibody levels increase about 10-fold with each additional injection.¹³ IgM antibody to hepatitis A can be detected shortly after the first or second injection.¹³

In the light of the safety and tolerability of the formalin-inactivated vaccine in more than 1200 adults and 400 children, we conducted a double-blind, placebo-controlled trial in a community of Hasidic Jewish children with a high rate of hepatitis A. The community is characterized by rapid growth and large families (averaging more than six members per family). Hepatitis A is primarily a childhood illness in this population; 68 percent of persons more than 19 years of age have detectable levels of antibody to the virus. ¹⁷ Previous epidemiologic studies have revealed strong

seasonal trends in incidence (peaking during the summer and winter) and a year-to-year repetition of hepatitis A epidemics. The occurrence of hepatitis A correlated with the presence of children three to five years old in a household and with a pattern of early schooling (from three years of age) in an environment similar to that of day-care centers.

METHODS

Vaccine and Placebo

The vaccine and placebo were prepared at Merck Research Laboratories (West Point, Pa.). The vaccine was prepared with modifications of a previously described technique¹² that make possible the large-scale manufacture of this vaccine. In brief, MRC-5 cell monolayers were established in a commercial medium (Nunc Cell Factories, Nunc, Roskilde, Denmark), infected with the attenuated strain CR326F', and maintained for several weeks by regular feeding. At the appropriate time, infected MRC-5 monolayers were lysed by exposure to detergent, and the antigen in the supernatant buffer was recovered by decantation and concentrated by ultrafiltration. Thereafter, the vaccine antigen was highly purified and inactivated with formalin according to essentially the same techniques as previously described. A single lot of aqueous vaccine adsorbed to aluminum hydroxide and stored at 2°C to 8°C was used in this study. Each 0.6-ml dose of vaccine contained 25 units of hepatitis A virus antigen on radioimmunoassay against a purifiedvirus reference standard. This dose was formerly expressed as 400 ng of virus antigen.^{9,13} Like the vaccine, each dose of the placebo aluminum hydroxide diluent — contained 300 μ g of aluminum and thimerosal at a 1:20,000 dilution.

Study Participants

The study protocol was approved by the Western Institutional Review Board (Olympia, Wash.). Children 2 to 16 years old at the time of prevaccination serologic screening who were residents of the Kiryas Joel community in Monroe, New York, and who were expected to be available for follow-up were enrolled after consent was obtained from their parents or guardians. Children were excluded if they were seropositive for hepatitis A antibodies, were immunodeficient, had had a seizure within the past year, were known to be allergic to any component of the vaccine, had received immune globulin during the 6 months before the study started, had received any other hepatitis A vaccine, had received any other vaccine within the previous 15 days, or had any other condition that the investigators judged might interfere with the evaluation of study objectives.

After the epidemiologic pattern of disease had been taken into account, vaccination was planned to begin in June 1991 to allow as many seronegative children as possible to seroconvert before the expected summer-fall outbreak.

After screening, seronegative children received a single 0.6-ml intramuscular injection containing either vaccine or placebo. Blood samples were obtained on the day of vaccination and one month later.

Randomization and Blinding

Children were assigned to receive vaccine or placebo according to a schedule for randomly assigning numbers that was based on the sequential order of injection. The randomization code was not revealed to any study personnel, the manufacturer's research staff for hepatitis A, or the participants and their parents or guardians until the termination of the study. When labeled with the numbers, the vials of vaccine and placebo were indistinguishable.

Monitoring of Adverse Reactions and Cases of Hepatitis A

Each participant was observed for at least 15 minutes after injection for any immediate allergic reactions. The parent or guardian was asked to record the child's oral temperature and any systemic

reactions or reactions at the injection site on a vaccination report card four hours after injection and daily for the next four days. Study personnel were to be notified immediately in case of any unexpected or severe reactions. If a report card was not returned on time, a report was obtained by telephone.

Clinically apparent cases of hepatitis A were detected both through active surveillance by semimonthly telephone calls to each child's parent or guardian and through direct reporting of possible cases by the parent or guardian. Children presenting with any signs or symptoms of hepatitis A were examined by the primary investigator, and a blood sample was obtained; this sample was tested for IgM antibody to hepatitis A virus, and serum alanine aminotransferase and total bilirubin were measured. Children were followed by study personnel until a definitive diagnosis was made and their illness had resolved.

Independent Monitoring Committee

An independent committee was appointed to monitor the progress of the trial, the safety and tolerability of the vaccine and placebo, and the accrual of cases of hepatitis A among the participants and to determine when the study should be terminated. The committee determined whether each clinical case reported met the case definition.

Case Definition

A clinical case of hepatitis A disease was defined by the following features: a diagnostic level of IgM antibody to the virus; a serum alanine aminotransferase level at least twice the upper limit of normal during an episode of illness, with no other obvious cause; and one or more of the clinical signs or symptoms consistent with hepatitis A — i.e., dermal, scleral, or faucial icterus associated with a serum total bilirubin level of at least 2.0 mg per deciliter (\geq 35 μ mol per liter), fatigue, malaise, abdominal pain, emesis, an oral temperature of 38.3°C or higher (\geq 101°F) without any other cause, clay-colored stools, or dark urine.

Evaluation of Efficacy

Interim analyses were planned by the monitoring committee so that the study could be stopped if efficacy was demonstrated. Clinical cases of hepatitis A occurring before the 50th day after the first injection were excluded from the primary analysis of efficacy in order to eliminate from consideration children who were already infected before the injection. Only clinical cases of disease that met the case definition and occurred 50 days after the first injection or later could be considered in any determination of whether to stop or continue the trial. The committee could stop the study if the lower bound of a one-sided 95 percent confidence-interval estimate of efficacy was 47.6 percent or more. The committee reserved the option to make a point estimate of efficacy after the trial ended; this estimate would include cases accrued at various times less than 50 days after injection, along with the corresponding 95 percent confidence interval (lower bound, one-sided).

Laboratory Studies

Serum samples from potential study participants were screened at Merck Research Laboratories for antibodies to hepatitis A by radioimmunoassay of the eluate of blood obtained by finger stick (20 µl) and collected on dried filter paper, according to a modified format^{11,13} (and unpublished data) of an assay for the hepatitis A virus antibody (HAVAB, Abbott Laboratories, North Chicago). During the blinded phase of the trial, serum from patients in whom hepatitis A was suspected was tested for IgM antibody to the virus (HAVAB-M, Abbott Laboratories) by an independent commercial laboratory, and the level of alanine aminotransferase and bilirubin was measured by this laboratory. Serum samples obtained on the day of the first injection and one month later were tested for hepatitis A antibody with the modified HAVAB assay11,13; the results were expressed in milli-International Units per milliliter, in accordance with the standard reference serum of the World Health Organization, and titers ≥10 mIU per milliliter were considered to show

seropositivity. All testing was done in a blinded manner at Merck Research Laboratories after the code was broken by the committee.

Statistical Analysis

The annual incidence of hepatitis A was estimated from epidemiologic data to be at least 3 percent among the children of this community. If the vaccine had an efficacy of 80 percent, enrolling 600 children in each study group would provide a power of 95 percent for rejecting the null hypothesis that the attack rates of hepatitis A disease would be equal in the vaccine and placebo groups.

Efficacy was calculated with the following formula: 1 — (observed attack rate in the vaccine recipients/observed attack rate in the placebo recipients). The attack rate in each group was calculated by dividing the number of children initially seronegative according to their antibody level on day 0 (or their status on screening, for the 77 children from whom a sample was not obtained on day 0) by the number of children with a confirmed clinical case of hepatitis A. To determine the confidence intervals for efficacy, the number of cases of clinical disease in each group was assumed to follow a Poisson distribution, with parameters lambda v for the vaccine group and lambda p for the placebo group. Under this assumption, the number of vaccine cases, V, has a binomial distribution (T,u) conditional on T, the total number of cases, with u = lambda v/(lambda v + lambda p). Exact confidence intervals were computed for u and transformed into confidence intervals for efficacy.

The Type I error rate for an interim analysis was less than 0.4 percent. If the true efficacy of the vaccine was 80 percent or 90 percent, an interim analysis would have a power of at least 53 percent or 85 percent, respectively, to detect a difference between the vaccine and placebo groups. In all other comparisons, a P value ≤0.05 was considered to denote statistical significance.

Contingency tables were analyzed with Fisher's exact test or a chi-square test.

RESULTS

From June 24 to November 5, 1991, 1037 children were enrolled in the trial; 519 children received one injection of vaccine, and 518 received one injection of placebo. Thirty-five percent of the children screened for the study were found to have detectable levels of hepatitis A antibody and were excluded. The vaccine and placebo groups were similar in sex ratio, age at first injection, and length of follow-up (Table 1).

Adverse Reactions

There were no serious adverse reactions during the study. Adverse reactions were mild and self-limited and consisted mainly of local reactions at the injection site (pain, tenderness, swelling, warmth, or rubor), occurring in 42 of the 515 vaccine recipients evaluated (8 percent) and 44 of the 510 placebo recipients evaluated (9 percent) (P = 0.82) within 24 hours of vaccination. Oral temperatures ≥38.3°C (≥101°F) were observed in five vaccine recipients and seven placebo recipients. No severe or fulminant cases of hepatitis A or deaths occurred during the trial.

Efficacy

A total of 34 clinical cases of hepatitis A (18 cases occurring ≥50 days after injection and 16 cases <50 days after injection) were reported through November 5, 1991. The monitoring committee met on November 6 for the first interim analysis of the data. The analysis showed that the vaccine had a high degree of efficacy, and the committee recommended that the study be

Table 1. Selected Characteristics of the Study Groups.*

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| Characteristic | VACCINE RECIPIENTS (N = 519) | PLACEBO RECIPIENTS (N = 518) |
|-----------------------------|------------------------------------|------------------------------------|
| Age at first injection (yr) | | |
| Mean | 7.99 | 7.84 |
| Median | 7.44 | 7.31 |
| Range | 2-16 | 2-16 |
| Sex (M/F) | 267/252 | 268/250 |
| Mean follow-up (days) | 104 | 102 |

^{*}None of the differences between the groups were significant.

terminated as soon as vaccine could be provided for the placebo recipients. Case accrual continued in a blinded fashion until November 19, 1991, when vaccination of the placebo recipients began. An additional 10 cases (7 diagnosed ≥50 days and 3 <50 days after injection) were reported from November 6 through November 18. The committee met again on December 12 to review the additional cases and reach a final assessment of the vaccine's efficacy. The final analysis of the 25 cases occurring ≥50 days after injection showed that all 25 cases occurred in placebo recipients and none in vaccine recipients (P<0.001) (Table 2 and Fig. 1).

All 25 placebo recipients with hepatitis A had IgM antibody to the virus, alanine aminotransferase levels more than twice the upper limit of normal (mean, 1383 U per liter; range, 240 to 2850 [mean, 23,511 nmol per second per liter; range, 4080 to 48,450]), and symptoms typical of the disease. Thirteen of the 25 children had icterus, confirmed by elevation of the serum bilirubin concentration. Among all placebo recipients, 3 cases occurred between days 5 and 18 after injection and 34 cases between days 21 and 137.

Among the vaccine recipients, seven cases occurred between days 5 and 18 after injection and none after day 21. All vaccine recipients with hepatitis A had IgM antibody to the virus, alanine aminotransferase levels more than twice the upper limit of normal (mean, 1579 U per liter; range, 196 to 4100 [mean,

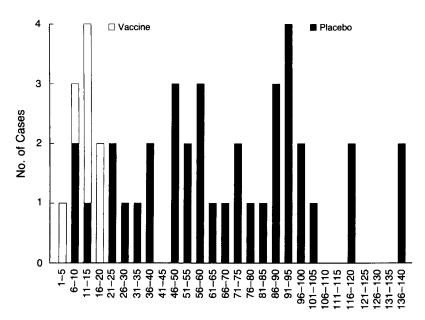
Table 2. Results of the Efficacy Analysis of Inactivated Hepatitis A Vaccine.*

| Days after Injection | Cases of | HEPATITIS A | EFFICACY ESTIMATE | P VALUE | 95% CI† |
|-------------------------|-----------|-------------|----------------------|---------|---------|
| | VACCINE | PLACEBO | | | |
| | cases/no. | evaluated‡ | % | | |
| 50-137 | 0/498 | 25/496 | 100 | < 0.001 | 87.3 |
| 21-46§ | 0/498 | 9/505 | | _ | _ |
| 5-18§ | 7/505 | 3/508 | | _ | _ |

^{*}Three vaccine recipients and one placebo recipient were excluded from this analysis because they had received immune globulin at their parents' request.

[†]CI denotes a one-sided confidence interval, lower bound.

[‡]Children initially seropositive according to modified HAVAB^{11,13} assay on day 0 are excluded from this table.



Days from Injection to Disease

Figure 1. Distribution of Cases of Clinical Hepatitis A in the Vaccine and Placebo Groups, According to the Length of Time since Injection.

26,843 nmol per second per liter; range, 3332 to 69,700]), and symptoms typical of the disease; three of the seven children had icterus.

Serologic Responses

Of the 305 initially seronegative vaccine recipients who were studied one month after vaccination and did not have clinical hepatitis A, all but 1 child had detectable antibody, with a geometric mean titer of 42 mIU per milliliter. Regression of the natural log titer on age showed a significant decrease in titer with increasing age (P<0.001).

DISCUSSION

The results of this randomized, double-blind trial confirm that the rapid induction of antibody (as measured by the neutralization test and radioimmunoassay) by this vaccine in previous studies correlates with protection against clinically apparent hepatitis A.4 Previous studies⁴ with the inactivated hepatitis A vaccine showed that the level of antibodies induced by one dose matched (and soon exceeded) the level measured three months after the administration of immune globulin, when there is still passive protection against clinically apparent disease. The correlation between the ability of the radioimmunoassay and that of the neutralization test³ to detect seropositivity developing after one injection of this vaccine in healthy young recipients is close to 100 percent three to four weeks after injection.¹³ Our study confirms that the antibody response associated with seroconversion parallels the start of protection. Similar seroconversion rates have been observed among adults given two doses of vaccine.15

The antigenicity of strains of hepatitis A virus from many sources has been found to be strongly

conserved. 19,20 Thus, the vaccine should prove protective against strains of all geographic origins.

The fact that an outbreak of hepatitis A was ongoing in the community before vaccination began does not permit precise determination of the minimal interval between vaccination and exposure to wild virus required to ensure protection against clinical disease. Some participants had probably been exposed and were in the incubation phase of the disease before they received the injection. This probably accounts for the cases that occurred in the vaccine recipients within the first three weeks after their inoculation. The best indicator of protection — a detectable antibody titer — has been documented as early as two weeks after one dose of vaccine.4,13 In studies of healthy adults, a second (booster) dose of vaccine at six months

has been shown to induce very high antibody titers, 14 with a decay curve predicting that high titers will persist for more than seven years (unpublished data). Studies being carried out two years after initial vaccination show that antibody levels continue to be high.

We plan to give participants in this study a booster dose after 6, 12, or 18 months. Although further studies of the long-term continuation of protection are ongoing, one study of natural cases of hepatitis A has suggested that otherwise healthy persons with prior exposure to the virus are protected from clinical disease after reexposure to the virus, even when their antibody titers have become undetectable.21 This suggests that after seroconversion, a single dose of vaccine might confer long-lasting protection against hepatitis A. No cases of hepatitis A with onset ≥21 days after injection have occurred among the vaccine recipients in this study during the 10-month follow-up period, although some cases have continued to occur among persons in the community who did not participate in the study, indicating that the virus was present.

Our study shows that this vaccine against hepatitis A prevents the clinical disease in children; it does not show whether the vaccine will also prevent subclinical infection. The only means by which subclinical infection could have been detected was repeated serologic monitoring of the levels of IgM antibody to the virus in the study participants. This obviously was not feasible in a trial conducted in children. At the one point before the end of the trial when blood was tested (one month after injection), only three cases of asymptomatic infection were detected in the placebo group a number inadequate for analysis.

The vaccine that we used should replace immune globulin as the agent for preexposure prophylaxis against hepatitis A and may merit trials for use in Vol. 327 No. 7

postexposure prophylaxis. Routine use of this vaccine in healthy, susceptible persons planning to visit areas with a high incidence of hepatitis A, children in day-care centers, members of groups at high risk, and food handlers could substantially decrease the morbidity and mortality associated with this disease. The early protection afforded by this vaccine should make it of special practical benefit to travelers, military personnel, and people who live in frequently affected communities.

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EXHIBIT 249

M-M-R[®] II (MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

DESCRIPTION

M-M-R[®] II (Measles, Mumps, and Rubella Virus Vaccine Live) is a live virus vaccine for vaccination against measles (rubeola), mumps, and rubella (German measles).

M-M-R II is a sterile lyophilized preparation of (1) ATTENUVAX® (Measles Virus Vaccine Live), a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; (2) MUMPSVAX® (Mumps Virus Vaccine Live), the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) MERUVAX® II (Rubella Virus Vaccine Live), the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts.{1.2}

The growth medium for measles and mumps is Medium 199 (a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum) containing SPGA (sucrose, phosphate, glutamate, and recombinant human albumin) as stabilizer and neomycin.

The growth medium for rubella is Minimum Essential Medium (MEM) [a buffered salt solution containing vitamins and amino acids and supplemented with fetal bovine serum] containing recombinant human albumin and neomycin. Sorbitol and hydrolyzed gelatin stabilizer are added to the individual virus harvests.

The cells, virus pools, and fetal bovine serum are all screened for the absence of adventitious agents.

The reconstituted vaccine is for subcutaneous administration. Each 0.5 mL dose contains not less than $1,000~TCID_{50}$ (tissue culture infectious doses) of measles virus; $12,500~TCID_{50}$ of mumps virus; and $1,000~TCID_{50}$ of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), recombinant human albumin (\leq 0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative.

Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.

CLINICAL PHARMACOLOGY

Measles, mumps, and rubella are three common childhood diseases, caused by measles virus, mumps virus (paramyxoviruses), and rubella virus (togavirus), respectively, that may be associated with serious complications and/or death. For example, pneumonia and encephalitis are caused by measles. Mumps is associated with aseptic meningitis, deafness and orchitis; and rubella during pregnancy may cause congenital rubella syndrome in the infants of infected mothers.

The impact of measles, mumps, and rubella vaccination on the natural history of each disease in the United States can be quantified by comparing the maximum number of measles, mumps, and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995. For measles, 894,134 cases reported in 1941 compared to 288 cases reported in 1995 resulted in a 99.97% decrease in reported cases; for mumps, 152,209 cases reported in 1968 compared to 840 cases reported in 1995 resulted in a 99.45% decrease in reported cases; and for rubella, 57,686 cases reported in 1969 compared to 200 cases reported in 1995 resulted in a 99.65% decrease.{3}

Clinical studies of 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II is highly immunogenic and generally well tolerated. In these studies, a single injection of the vaccine induced measles hemagglutination-inhibition (HI) antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible persons. However, a small percentage (1-5%) of vaccinees may fail to seroconvert after the primary dose (see also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*).

A study{4} of 6-month-old and 15-month-old infants born to vaccine-immunized mothers demonstrated that, following vaccination with ATTENUVAX, 74% of the 6-month-old infants developed detectable neutralizing antibody (NT) titers while 100% of the 15-month-old infants developed NT. This rate of seroconversion is higher than that previously reported for 6-month-old infants born to naturally immune mothers tested by HI assay. When the 6-month-old infants of immunized mothers were revaccinated at 15

months, they developed antibody titers equivalent to the 15-month-old vaccinees. The lower seroconversion rate in 6-month-olds has two possible explanations: 1) Due to the limit of the detection level of the assays (NT and enzyme immunoassay [EIA]), the presence of trace amounts of undetectable maternal antibody might interfere with the seroconversion of infants; or 2) The immune system of 6-month-olds is not always capable of mounting a response to measles vaccine as measured by the two antibody assays.

There is some evidence to suggest that infants who are born to mothers who had wild-type measles and who are vaccinated at less than one year of age may not develop sustained antibody levels when later revaccinated. The advantage of early protection must be weighed against the chance for failure to respond adequately on reimmunization. {5,6}

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled field trials which demonstrated a high degree of protective efficacy afforded by the individual vaccine components. (7-12) These studies also established that seroconversion in response to vaccination against measles, mumps, and rubella paralleled protection from these diseases. (13-15)

Following vaccination, antibodies associated with protection can be measured by neutralization assays, HI, or ELISA (enzyme linked immunosorbent assay) tests. Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination. [16-18] See INDICATIONS AND USAGE, Non-Pregnant Adolescent and Adult Females, for Rubella Susceptibility Testing.

The RA 27/3 rubella strain in M-M-R II elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine{19-25} and has been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies.{26,27} The RA 27/3 rubella strain immunologically simulates natural infection more closely than other rubella vaccine viruses.{27-29} The increased levels and broader profile of antibodies produced by RA 27/3 strain rubella virus vaccine appear to correlate with greater resistance to subclinical reinfection with the wild virus,{27,29-31} and provide greater confidence for lasting immunity.

INDICATIONS AND USAGE

Recommended Vaccination Schedule

M-M-R II is indicated for simultaneous vaccination against measles, mumps, and rubella in individuals 12 months of age or older.

Individuals first vaccinated at 12 months of age or older should be revaccinated prior to elementary school entry. Revaccination is intended to seroconvert those who do not respond to the first dose. The Advisory Committee on Immunization Practices (ACIP) recommends administration of the first dose of M-M-R II at 12 to 15 months of age and administration of the second dose of M-M-R II at 4 to 6 years of age.{32} In addition, some public health jurisdictions mandate the age for revaccination. Consult the complete text of applicable guidelines regarding routine revaccination including that of high-risk adult populations.

Measles Outbreak Schedule

Infants Between 6 to 12 Months of Age

Local health authorities may recommend measles vaccination of infants between 6 to 12 months of age in outbreak situations. This population may fail to respond to the components of the vaccine. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. The younger the infant, the lower the likelihood of seroconversion (see CLINICAL PHARMACOLOGY). Such infants should receive a second dose of M-M-R II between 12 to 15 months of age followed by revaccination at elementary school entry.{32}

Unnecessary doses of a vaccine are best avoided by ensuring that written documentation of vaccination is preserved and a copy given to each vaccinee's parent or guardian.

Other Vaccination Considerations

Non-Pregnant Adolescent and Adult Females

Immunization of susceptible non-pregnant adolescent and adult females of childbearing age with live attenuated rubella virus vaccine is indicated if certain precautions are observed (see below and PRECAUTIONS). Vaccinating susceptible postpubertal females confers individual protection against subsequently acquiring rubella infection during pregnancy, which in turn prevents infection of the fetus and consequent congenital rubella injury.{33}

Women of childbearing age should be advised not to become pregnant for 3 months after vaccination and should be informed of the reasons for this precaution.

The ACIP has stated "If it is practical and if reliable laboratory services are available, women of childbearing age who are potential candidates for vaccination can have serologic tests to determine susceptibility to rubella. However, with the exception of premarital and prenatal screening, routinely performing serologic tests for all women of childbearing age to determine susceptibility (so that vaccine is given only to proven susceptible women) can be effective but is expensive. Also, 2 visits to the health-care provider would be necessary— one for screening and one for vaccination. Accordingly, rubella vaccination of a woman who is not known to be pregnant and has no history of vaccination is justifiable without serologic testing— and may be preferable, particularly when costs of serology are high and follow-up of identified susceptible women for vaccination is not assured."{33}

Postpubertal females should be informed of the frequent occurrence of generally self-limited arthralgia and/or arthritis beginning 2 to 4 weeks after vaccination (see ADVERSE REACTIONS). *Postpartum Women*

It has been found convenient in many instances to vaccinate rubella-susceptible women in the immediate postpartum period (see PRECAUTIONS, *Nursing Mothers*).

Other Populations

Previously unvaccinated children older than 12 months who are in contact with susceptible pregnant women should receive live attenuated rubella vaccine (such as that contained in monovalent rubella vaccine or in M-M-R II) to reduce the risk of exposure of the pregnant woman.

Individuals planning travel outside the United States, if not immune, can acquire measles, mumps, or rubella and import these diseases into the United States. Therefore, prior to international travel, individuals known to be susceptible to one or more of these diseases can either receive the indicated monovalent vaccine (measles, mumps, or rubella), or a combination vaccine as appropriate. However, M-M-R II is preferred for persons likely to be susceptible to mumps and rubella; and if monovalent measles vaccine is not readily available, travelers should receive M-M-R II regardless of their immune status to mumps or rubella.{34-36}

Vaccination is recommended for susceptible individuals in high-risk groups such as college students, health-care workers, and military personnel. [33,34,37]

According to ACIP recommendations, most persons born in 1956 or earlier are likely to have been infected with measles naturally and generally need not be considered susceptible. All children, adolescents, and adults born after 1956 are considered susceptible and should be vaccinated, if there are no contraindications. This includes persons who may be immune to measles but who lack adequate documentation of immunity such as: (1) physician-diagnosed measles, (2) laboratory evidence of measles immunity, or (3) adequate immunization with live measles vaccine on or after the first birthday.{34}

The ACIP recommends that "Persons vaccinated with inactivated vaccine followed within 3 months by live vaccine should be revaccinated with two doses of live vaccine. Revaccination is particularly important when the risk of exposure to wild-type measles virus is increased, as may occur during international travel." {34}

Post-Exposure Vaccination

Vaccination of individuals exposed to wild-type measles may provide some protection if the vaccine can be administered within 72 hours of exposure. If, however, vaccine is given a few days before exposure, substantial protection may be afforded.{34,38,39} There is no conclusive evidence that vaccination of individuals recently exposed to wild-type mumps or wild-type rubella will provide protection.{33,37}

Use With Other Vaccines

See DOSAGE AND ADMINISTRATION, Use With Other Vaccines.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including gelatin. (40)

Do not give M-M-R II to pregnant females; the possible effects of the vaccine on fetal development are unknown at this time. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and PRECAUTIONS, *Pregnancy*).

Anaphylactic or anaphylactoid reactions to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Febrile respiratory illness or other active febrile infection. However, the ACIP has recommended that all vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper respiratory infection with or without low-grade fever, or other low-grade febrile illness.{41}

Patients receiving immunosuppressive therapy. This contraindication does not apply to patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems.

Primary and acquired immunodeficiency states, including patients who are immunosuppressed in association with AIDS or other clinical manifestations of infection with human immunodeficiency viruses;{41-43} cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis{44} (MIBE), pneumonitis{45} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in immunocompromised individuals inadvertently vaccinated with measles-containing vaccine.

Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

WARNINGS

Due caution should be employed in administration of M-M-R II to persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevation which may occur following vaccination (see ADVERSE REACTIONS).

Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution, having adequate treatment on hand should a reaction occur (see PRECAUTIONS).{46}

However, the AAP has stated, "Most children with a history of anaphylactic reactions to eggs have no untoward reactions to measles or MMR vaccine. Persons are not at increased risk if they have egg allergies that are not anaphylactic, and they should be vaccinated in the usual manner. In addition, skin testing of egg-allergic children with vaccine has not been predictive of which children will have an immediate hypersensitivity reaction...Persons with allergies to chickens or chicken feathers are not at increased risk of reaction to the vaccine."{47}

Hypersensitivity to Neomycin

The AAP states, "Persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive measles vaccine. Most often, however, neomycin allergy manifests as a contact dermatitis, which is a delayed-type (cell-mediated) immune response rather than anaphylaxis. In such persons, an adverse reaction to neomycin in the vaccine would be an erythematous, pruritic nodule or papule, 48 to 96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving measles vaccine." [47]

Thrombocytopenia

Individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia with the first dose of M-M-R II (or its component vaccines) may develop thrombocytopenia with repeat doses. Serologic status may be evaluated to determine whether or not additional doses of vaccine are needed. The potential risk to benefit ratio should be carefully evaluated before considering vaccination in such cases (see ADVERSE REACTIONS).

PRECAUTIONS

General

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Special care should be taken to ensure that the injection does not enter a blood vessel.

Children and young adults who are known to be infected with human immunodeficiency viruses and are not immunosuppressed may be vaccinated. However, vaccinees who are infected with HIV should be monitored closely for vaccine-preventable diseases because immunization may be less effective than for uninfected persons (see CONTRAINDICATIONS).{42,43}

Vaccination should be deferred for 3 months or longer following blood or plasma transfusions, or administration of immune globulin (human).{47}

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.{33} However, transmission of the rubella vaccine virus to infants via breast milk has been documented (see *Nursing Mothers*).

There are no reports of transmission of live attenuated measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R II.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine; {48} no studies have been reported to date of the effect of measles virus vaccines on untreated tuberculous children. However, individuals with active untreated tuberculosis should not be vaccinated.

As for any vaccine, vaccination with M-M-R II may not result in protection in 100% of vaccinees.

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of M-M-R II or other measles-, mumps-, or rubella-containing vaccines.

Information for Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health-care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Patients, parents, or guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.{49}

Pregnancy should be avoided for 3 months following vaccination, and patients should be informed of the reasons for this precaution (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, CONTRAINDICATIONS, and PRECAUTIONS, *Pregnancy*). *Laboratory Tests*

See INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females*, for Rubella Susceptibility Testing, and CLINICAL PHARMACOLOGY. *Drug Interactions*

See DOSAGE AND ADMINISTRATION, Use With Other Vaccines. Immunosuppressive Therapy

The immune status of patients about to undergo immunosuppressive therapy should be evaluated so that the physician can consider whether vaccination prior to the initiation of treatment is indicated (see CONTRAINDICATIONS and PRECAUTIONS).

The ACIP has stated that "patients with leukemia in remission who have not received chemotherapy for at least 3 months may receive live virus vaccines. Short-term (<2 weeks), low- to moderate-dose systemic corticosteroid therapy, topical steroid therapy (e.g. nasal, skin), long-term alternate-day treatment with low to moderate doses of short-acting systemic steroid, and intra-articular, bursal, or tendon injection of corticosteroids are not immunosuppressive in their usual doses and do not contraindicate the administration of [measles, mumps, or rubella vaccine]."{33,34,37} Immune Globulin

Administration of immune globulins concurrently with M-M-R II may interfere with the expected immune response. {33,34,47}

See also PRECAUTIONS, General.

Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II has not been evaluated for carcinogenic or mutagenic potential, or potential to impair fertility. Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with M-M-R II. It is also not known whether M-M-R II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for 3 months following vaccination (see INDICATIONS AND USAGE, *Non-Pregnant Adolescent and Adult Females* and CONTRAINDICATIONS).

In counseling women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of vaccination, the physician should be aware of the following: (1) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome; (50) (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans; (37) and (3) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects and prematurity have been observed subsequent to infection with wild-type measles during pregnancy. (51,52) There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy. However, it would be prudent to assume that the vaccine strain of virus is also capable of inducing adverse fetal effects. *Nursing Mothers*

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating postpartum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants.{53} In the infants with serological evidence of rubella infection, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella.{54,55} Caution should be exercised when M-M-R II is administered to a nursing woman. *Pediatric Use*

Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established (see also CLINICAL PHARMACOLOGY). Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established. *Geriatric Use*

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The following adverse reactions are listed in decreasing order of severity, without regard to causality, within each body system category and have been reported during clinical trials, with use of the marketed vaccine, or with use of monovalent or bivalent vaccine containing measles, mumps, or rubella:

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Endocrine System

Diabetes mellitus.

Hemic and Lymphatic System

Thrombocytopenia (see WARNINGS, *Thrombocytopenia*); purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis and anaphylactoid reactions have been reported as well as related phenomena such as angioneurotic edema (including peripheral or facial edema) and bronchial spasm in individuals with or without an allergic history.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Arthralgia and/or arthritis (usually transient and rarely chronic), and polyneuritis are features of infection with wild-type rubella and vary in frequency and severity with age and sex, being greatest in adult females and least in prepubertal children. This type of involvement as well as myalgia and paresthesia, have also been reported following administration of MERUVAX II.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Only rarely have vaccine recipients developed chronic joint symptoms.

Following vaccination in children, reactions in joints are uncommon and generally of brief duration. In women, incidence rates for arthritis and arthralgia are generally higher than those seen in children (children: 0-3%; women: 12-26%),{17,56,57} and the reactions tend to be more marked and of longer duration. Symptoms may persist for a matter of months or on rare occasions for years. In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and in adult women. Even in women older than 35 years, these reactions are generally well tolerated and rarely interfere with normal activities.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) (see CONTRAINDICATIONS); subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines.

The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases). (58,59)

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported (see CONTRAINDICATIONS). In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with infection with wild-type measles, 6-22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study conducted by the Centers for Disease Control and Prevention suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.{60}

Cases of aseptic meningitis have been reported to VAERS following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Respiratory System

Pneumonia; pneumonitis (see CONTRAINDICATIONS); sore throat; cough; rhinitis. Skin

Stevens-Johnson syndrome; erythema multiforme; urticaria; rash; measles-like rash; pruritis.

Local reactions including burning/stinging at injection site; wheal and flare; redness (erythema); swelling; induration; tenderness; vesiculation at injection site; Henoch-Schönlein purpura; acute hemorrhagic edema of infancy.

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; retrobulbar neuritis; conjunctivitis.

Urogenital System

Epididymitis; orchitis.

Other

Death from various, and in some cases unknown, causes has been reported rarely following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals (see CONTRAINDICATIONS). No deaths or permanent sequelae were reported in a published post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993.{61}

Under the National Childhood Vaccine Injury Act of 1986, health-care providers and manufacturers are required to record and report certain suspected adverse events occurring within specific time periods after vaccination. However, the U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) which will accept all reports of suspected events. [49] A VAERS report form as well as information regarding reporting requirements can be obtained by calling VAERS 1-800-822-7967.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravascularly.

The dose for any age is 0.5 mL administered subcutaneously, preferably into the outer aspect of the upper arm.

The recommended age for primary vaccination is 12 to 15 months.

Revaccination with M-M-R II is recommended prior to elementary school entry. See also INDICATIONS AND USAGE, *Recommended Vaccination Schedule*.

Children first vaccinated when younger than 12 months of age should receive another dose between 12 to 15 months of age followed by revaccination prior to elementary school entry. [32] See also INDICATIONS AND USAGE, Measles Outbreak Schedule.

Immune Globulin (IG) is not to be given concurrently with M-M-R II (see PRECAUTIONS, *General* and PRECAUTIONS, *Drug Interactions*).

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, 5/8" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial — First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. If the lyophilized vaccine cannot be dissolved, discard. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. M-M-R II, when reconstituted, is clear yellow. *Use With Other Vaccines*

M-M-R II should be given one month before or after administration of other live viral vaccines.

M-M-R II has been administered concurrently with VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)], and PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] using separate injection sites and syringes. No impairment of immune response to individually tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed with M-M-R II were similar to those seen when each vaccine was given alone.

Routine administration of DTP (diphtheria, tetanus, pertussis) and/or OPV (oral poliovirus vaccine) concurrently with measles, mumps and rubella vaccines is not recommended because there are limited data relating to the simultaneous administration of these antigens.

However, other schedules have been used. The ACIP has stated "Although data are limited concerning the simultaneous administration of the entire recommended vaccine series (i.e., DTaP [or DTwP], IPV [or OPV], Hib with or without Hepatitis B vaccine, and varicella vaccine), data from numerous studies have indicated no interference between routinely recommended childhood vaccines (either live, attenuated, or killed). These findings support the simultaneous use of all vaccines as recommended." [62]

HOW SUPPLIED

No. 4681 — M-M-R II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC** 0006-4681-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature. Storage

To maintain potency, M-M-R II must be stored between -58°F and +46°F (-50°C to +8°C). Use of dry ice may subject M-M-R II to temperatures colder than -58°F (-50°C).

Protect the vaccine from light at all times, since such exposure may inactivate the viruses.

Before reconstitution, store the lyophilized vaccine at 36°F to 46°F (2°C to 8°C). The diluent may be stored in the refrigerator with the lyophilized vaccine or separately at room temperature. **Do not freeze the** diluent

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial in a dark place at 36°F to 46°F (2°C to 8°C) and discard if not used within 8 hours.

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

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Revised: XX/XXXX

uspi-v205c-i-XXXXrXXX

Case 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 343 of 497 Use caution when administering M-M-R II to individuals with

These highlights do not include all the information needed to use M-M-R II safely and effectively. See full prescribing information for M-M-R II.

M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) Suspension for subcutaneous injection Initial U.S. Approv al: 1978

-----INDICATIONS AND USAGE-

M-M-R II is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older. (1)

--- DOSAGE AND ADMINISTRATION-

Administer a 0.5-mL dose of M-M-R II subcutaneously. (2.1)

- The first dose is administered at 12 to 15 months of age. (2.1)
- The second dose is administered at 4 to 6 years of age. (2.1)

----DOSAGE FORMS AND STRENGTHS --

Suspension for injection (0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using accompanying sterile diluent. (3)

- CONTRAINDICATIONS -

- Hypersensitivity to any component of the vaccine. (4.1)
- Immunosuppression. (4.2)
- Moderate or severe febrile illness. (4.3)
- Active untreated tuberculosis. (4.4)
- Pregnancy. (4.5, 8.1)

---- WARNINGS AND PRECAUTIONS ---

 Use caution when administering M-M-R II to individuals with a history of febrile seizures. (5.1)

- Use caution when administering M-M-R II to individuals with anaphylaxisor immediate hypersensitivity following egg ingestion. (5.2)
- Use caution when administering M-M-R II to individuals with a history of thrombocytopenia. (5.3)
- Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II. (5.4, 7.2)

---ADVERSE REACTIONS--

See full prescribing information for adverse reactions occurring during clinical trials or the post-marketing period. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---DRUG INTERACTIONS -

- Administration of immune globulins and other blood products concurrently with M-M-R II vaccine may interfere with the expected immune response. (7.2)
- M-M-R II vaccination may result in a temporary depression of purified protein derivative (PPD) tuberculin skin sensitivity. (7.3)

- USE IN SPECIFIC POPULATIONS-

 Pregnancy: Do not administer M-M-R II to females who are pregnant. Pregnancy should be avoided for 1 month following vaccination with M-M-R II. (4.5, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 06/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

M-M-R® II is a vaccine indicated for active immunization for the prevention of measles, mumps, and rubella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION

For subcutaneous use only.

2.1 Dose and Schedule

Each 0.5 mL dose is administered subcutaneously.

The first dose is administered at 12 to 15 months of age. A second dose is administered at 4 to 6 years of age.

The second dose may be administered prior to 4 years of age, provided that there is a minimum interval of one month between the doses of measles, mumps and rubella virus vaccine, live {1-2}.

Children who received an initial dose of measles, mumps and rubella vaccine prior to their first birthday should receive additional doses of vaccine at 12-15 months of age and at 4-6 years of age to complete the vaccination series [see Clinical Studies (14.2)].

For post-exposure prophylaxis for measles, administer a dose of M-M-R II vaccine within 72 hours after exposure.

2.2 Preparation and Administration

Use a sterile syringe free of preservatives, antiseptics, and detergents for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. To reconstitute, use only the diluent supplied with the vaccine since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Withdraw the entire volume of the supplied diluent from its vial and inject into lyophilized vaccine vial. Agitate to dissolve completely. Discard if the lyophilized vaccine cannot be dissolved.

Withdraw the entire volume of the reconstituted vaccine and inject subcutaneously into the outer aspect of the upper arm (deltoid region) or into the higher anterolateral area of the thigh.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug, when reconstituted, is a clear yellow liquid. Discard if particulate matter or discoloration are observed in the reconstituted vaccine.

To minimize loss of potency, administer M-M-R II as soon as possible after reconstitution. If not used immediately, the reconstituted vaccine may be stored between 36°F to 46°F (2°C to 8°C), protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

3 DOSAGE FORMS AND STRENGTHS

M-M-R II vaccine is a suspension for injection supplied as a single dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent [see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]. A single dose after reconstitution is 0.5 mL.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer M-M-R II vaccine to individuals with a history of hypersensitivity to any component of the vaccine (including gelatin) {3} or who have experienced a hypersensitivity reaction following administration of a previous dose of M-M-R II vaccine or any other measles, mumps and rubella-containing vaccine. Do not administer M-M-R II vaccine to individuals with a history of anaphylaxis to neomycin [see Description (11)].

4.2 Immunosuppression

Do not administer M-M-R II vaccine to individuals who are immunodeficient or immunosuppressed due to disease or medical therapy. Measles inclusion body encephalitis {4} (MIBE), pneumonitis {5} and death as a direct consequence of disseminated measles vaccine virus infection have been reported in

immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

Do not administer M-M-R II to individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated.

4.3 Moderate or Severe Febrile Illness

Do not administer M-M-R II vaccine to individuals with an active febrile illness with fever >101.3°F (>38.5°C).

4.4 Active Untreated Tuberculosis

Do not administer M-M-R II vaccine to individuals with active untreated tuberculosis (TB).

4.5 Pregnancy

Do not administer M-M-R II to individuals who are pregnant or who are planning on becoming pregnant within the next month [see Use in Specific Populations (8.1) and Patient Counseling Information (17)].

5 WARNINGS AND PRECAUTIONS

5.1 Febrile Seizure

There is a risk of fever and associated febrile seizure in the first 2 weeks following immunization with M-M-R II vaccine. For children who have experienced a previous febrile seizure (from any cause) and those with a family history of febrile seizures there is a small increase in risk of febrile seizure following receipt of M-M-R II vaccine [see Adverse Reactions (6)].

5.2 Hypersensitivity to Eggs

Individuals with a history of anaphylactic, anaphylactoid, or other immediate reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving M-M-R II vaccine. The potential risks and known benefits should be evaluated before considering vaccination in these individuals.

5.3 Thrombocytopenia

Transient thrombocytopenia has been reported within 4-6 weeks following vaccination with measles, mumps and rubella vaccine. Carefully evaluate the potential risk and benefit of vaccination in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of measles, mumps, and rubella vaccine {6-8} [see Adverse Reactions (6)].

5.4 Immune Globulins and Transfusions

Immune Globulins (IG) and other blood products should not be given concurrently with M-M-R II [see Drug Interactions (7.2)]. These products may contain antibodies that interfere with vaccine virus replication and decrease the expected immune response.

The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

6 ADVERSE REACTIONS

The following adverse reactions include those identified during clinical trials or reported during post-approval use of M-M-R II vaccine or its individual components.

Body as a Whole

Panniculitis; atypical measles; fever; syncope; headache; dizziness; malaise; irritability.

Cardiovascular System

Vasculitis.

Digestive System

Pancreatitis; diarrhea; vomiting; parotitis; nausea.

Hematologic and Lymphatic Systems

Thrombocytopenia; purpura; regional lymphadenopathy; leukocytosis.

Immune System

Anaphylaxis, anaphylactoid reactions, angioedema (including peripheral or facial edema) and bronchial spasm.

Musculoskeletal System

Arthritis; arthralgia; myalgia.

Nervous System

Encephalitis; encephalopathy; measles inclusion body encephalitis (MIBE) subacute sclerosing panencephalitis (SSPE); Guillain-Barré Syndrome (GBS); acute disseminated encephalomyelitis (ADEM); transverse myelitis; febrile convulsions; afebrile convulsions or seizures; ataxia; polyneuritis; polyneuropathy; ocular palsies; paresthesia.

Respiratory System

Pneumonia; pneumonitis; sore throat; cough; rhinitis.

Skin

Stevens-Johnson syndrome; acute hemorrhagic edema of infancy; Henoch-Schönlein purpura; erythema multiforme; urticaria; rash; measles-like rash; pruritus; injection site reactions (pain, erythema, swelling and vesiculation).

Special Senses — Ear

Nerve deafness; otitis media.

Special Senses — Eye

Retinitis; optic neuritis; papillitis; conjunctivitis.

Urogenital System Epididymitis; orchitis.

7 DRUG INTERACTIONS

7.1 Corticosteroids and Immunosuppressive Drugs

M-M-R II vaccine should not be administered to individuals receiving immunosuppressive therapy, including high dose corticosteroids. Vaccination with M-M-R II vaccine can result in disseminated disease due to measles vaccine in individuals on immunosuppressive drugs [see Contraindications (4.2)].

7.2 Immune Globulins and Transfusions

Administration of immune globulins and other blood products concurrently with M-M-R II vaccine may interfere with the expected immune response {9-11} [see Warnings and Precautions (5.4)]. The ACIP has specific recommendations for intervals between administration of antibody containing products and live virus vaccines.

7.3 Tuberculin Skin Testing

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin skin test with tuberculin purified protein derivative (PPD) is to be done, it should be administered before, simultaneously with, or at least 4 to 6 weeks after vaccination with M-M-R II vaccine.

7.4 Use with Other Live Viral Vaccines

M-M-R II vaccine can be administered concurrently with other live viral vaccines. If not given concurrently, M-M-R II vaccine should be given one month before or one month after administration of other live viral vaccines to avoid potential for immune interference.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

M-M-R II vaccine is contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses has been associated with maternal and fetal adverse outcomes.

Increased rates of spontaneous abortion, stillbirth, premature delivery and congenital defects have been observed following infection with wild-type measles during pregnancy. {12,13} Wild-type mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion.

Infection with wild-type rubella during pregnancy can lead to miscarriage or stillbirth. If rubella infection occurs during the first trimester of pregnancy, it can result in severe congenital defects, Congenital Rubella Syndrome (CRS). Congenital rubella syndrome in the infant includes but is not limited to eye manifestations (cataracts, glaucoma, retinitis), congenital heart defects, hearing loss, microcephaly, and intellectual disabilities. M-M-R II vaccine contains live attenuated measles, mumps and rubella viruses. It is not known whether M-M-R II vaccine can cause fetal harm when administered to pregnant woman. There are no adequate and well-controlled studies of M-M-R II vaccine administration to pregnant women.

All pregnancies have a risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data suggest the rates of major birth defects and miscarriage in women who received M-M-R II vaccine within 30 days prior to pregnancy or during pregnancy are consistent with estimated background rates (see Data).

Data

<u>Human Data</u>

A cumulative assessment of post-marketing reports for M-M-R II vaccine from licensure 01 April 1978 through 31 December 2018, identified 796 reports of inadvertent administration of M-M-R II vaccine occurring 30 days before or at any time during pregnancy with known pregnancy outcomes. Of the prospectively followed pregnancies for whom the timing of M-M-R II vaccination was known, 425 women received M-M-R II vaccine during the 30 days prior to conception through the second trimester. The outcomes for these 425 prospectively followed pregnancies included 16 infants with major birth defects, 4 cases of fetal death and 50 cases of miscarriage. No abnormalities compatible with congenital rubella syndrome have been identified in patients who received M-M-R II vaccine. Rubella vaccine virus es can cross the placenta, leading to asymptomatic infection of the fetus. Mumps vaccine virus has also been shown to infect the placenta {14}, but there is no evidence that it causes congenital malformations or disease in the fetus or infant.

The CDC established the Vaccine in Pregnancy registry (1971-1989) of women who had received rubella vaccines within 3 months before or after conception. Data on 1221 inadvertently vaccinated pregnant women demonstrated no evidence of an increase in fetal abnormalities or cases of Congenital Rubella Syndrome (CRS) in the enrolled women {15}.

8.2 Lactation

Risk Summary

It is not known whether measles or mumps vaccine virus is secreted in human milk. Studies have shown that lactating postpartum women vaccinated with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. {16,17} In the breast-fed infants with serological evidence of rubella virus vaccine strain antibodies, none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. {18,19}

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for M-M-R II, and any potential adverse effects on the breastfed child from M-M-R II or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

M-M-R II vaccine is not approved for individuals less than 12 months of age. Safety and effectiveness of measles vaccine in infants below the age of 6 months have not been established [see Clinical Studies (14)]. Safety and effectiveness of mumps and rubella vaccine in infants less than 12 months of age have not been established.

8.5 Geriatric Use

Clinical studies of M-M-R II did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 Description

M-M-R II vaccine is a sterile lyophilized preparation of (1) Measles Virus Vaccine Live, an attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embry o cell culture; (2) Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; and (3) Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts. {20,21} The cells, virus pools, recombinant human serum albumin and fetal bovine serum used in manufacturing are tested and determined to be free of adventitious agents.

After reconstitution, each 0.5 mL dose contains not less than 3.0 \log_{10} TCID₅₀ (tissue culture infectious doses) of measles virus; 4.1 \log_{10} TCID₅₀ of mumps virus; and 3.0 \log_{10} TCID₅₀ of rubella virus.

Each dose is calculated to contain sorbitol (14.5 mg), sucrose (1.9 mg), hydrolyzed gelatin (14.5 mg), recombinant human albumin (≤0.3 mg), fetal bovine serum (<1 ppm), approximately 25 mcg of neomy cin and other buffer and media ingredients. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

M-M-R II vaccination induces antibodies to measles, mumps, and rubella associated with protection which can be measured by neutralization assays, hemagglutination-inhibition (HI) assays, or enzyme linked immunosorbent assay (ELISA) tests. Results from efficacy studies or effectiveness studies that were previously conducted for the component vaccines of M-M-R II were used to define levels of serum antibodies that correlated with protection against measles, numps, and rubella [see Clinical Studies (14)].

12.6 Persistence of Antibody Responses After Vaccination

Neutralizing and ELISA antibodies to measles, mumps, and rubella viruses are still detectable in 95-100%, 74-91%, and 90-100% of individuals respectively, 11 to 13 years after primary vaccination. {22-28}

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

M-M-R II vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

Efficacy of measles, mumps, and rubella vaccines was established in a series of double-blind controlled trials. {29-34} These studies also established that seroconversion in response to vaccination against measles, mumps and rubella paralleled protection. {35-38}

14.2 Immunogenicity

Clinical studies enrolling 284 triple seronegative children, 11 months to 7 years of age, demonstrated that M-M-R II vaccine is immunogenic. In these studies, a single injection of the vaccine induced measles HI antibodies in 95%, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99% of susceptible individuals.

A study of 6-month-old and 15-month-old infants born to mothers vaccinated with a measles vaccine in childhood, demonstrated that, following infant and toddler vaccination with Measles Virus Vaccine, Live (previously US-licensed, manufactured by Merck), 74% of the 6-month-old infants developed detectable neutralizing antibody titers while 100% of the 15-month-old infants vaccinated with Measles Virus Vaccine, Live or M-M-R II vaccine developed neutralizing antibodies {39}. When the 6-month-old infants of immunized mothers were revaccinated at 15 months with M-M-R II vaccine, they developed antibody titers similar to those of toddlers who were vaccinated previously at 15-months of age.

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16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4681 — M-M-R II vaccine is supplied as follows:

(1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4681-00

(2) a box of 10 vials of diluent (package B)

Exposure to light may inactivate the vaccine viruses.

Before reconstitution, refrigerate the lyophilized vaccine at 36°F to 46°F, (2°C to 8°C).

Store accompanying diluent in the refrigerator with the lyophilized vaccine or separately at room temperature (68° to 77°F, 20° to 25°C). **Do not freeze the diluent**.

Administer M-M-R II vaccine as soon as possible after reconstitution. If not administered immediately, reconstituted vaccine may be stored between 36°F to 46°F (2°C to 8°C), protected from light, for up to 8 hours. Discard reconstituted vaccine if it is not used within 8 hours.

For information regarding the product or questions regarding storage conditions, call 1-800-MERCK-90 (1-800-637-2590).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Package Insert).

Discuss the following with the patient:

- Provide the required vaccine information to the patient, parent, or guardian.
- Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.
- Question the patient, parent, or guardian about reactions to a previous dose of M-M-R II vaccine or other measles-, mumps-, or rubella-containing vaccines.
- Question females of reproductive potential regarding the possibility of pregnancy. Inform female patients to avoid pregnancy for 1 month following vaccination [see Contraindications (4.5) and Use in Specific Populations (8.1)].
- Inform the patient, parent, or guardian that vaccination with M-M-R II may not offer 100% protection from measles, mumps, and rubella infection.
- Instruct patients, parents, or guardians to report any adverse reactions to their health-care provider. The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at https://www.vaers.hhs.gov.

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For patent information: www.merck.com/product/patent/home.html

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EXHIBIT 250

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VARIVAX safely and effectively. See full prescribing information for VARIVAX.

VARIVAX®

Varicella Virus Vaccine Live Suspension for subcutaneous injection Initial U.S. Approval: 1995

-----INDICATIONS AND USAGE -----

VARIVAX is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older. (1)

----- DOSAGE AND ADMINISTRATION -----

Each dose is approximately 0.5 mL after reconstitution and is administered by subcutaneous injection. (2.1)

Children (12 months to 12 years of age)

• If a second dose is administered, there should be a minimum interval of 3 months between doses. (2.1)

Adolescents (≥13 years of age) and Adults

 Two doses, to be administered a minimum of 4 weeks apart. (2.1)

---- DOSAGE FORMS AND STRENGTHS -----

Suspension for injection (approximately 0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using the accompanying sterile diluent. (2.2, 3, 16)

-----CONTRAINDICATIONS -----

- History of severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of varicella vaccine. (4.1)
- Primary or acquired immunodeficiency states. (4.2)
- Any febrile illness or active infection, including untreated tuberculosis. (4.3)
- Pregnancy. (4.4, 8.1, 17)

------ WARNINGS AND PRECAUTIONS-----

- Evaluate individuals for immune competence prior to administration of VARIVAX if there is a family history of congenital or hereditary immunodeficiency. (5.2)
- Avoid contact with high-risk individuals susceptible to varicella because of possible transmission of varicella vaccine virus. (5.4)

- Defer vaccination for at least 5 months following blood or plasma transfusions, or administration of immune globulins (IG). (5.5, 7.2)
- Avoid use of salicylates for 6 weeks following administration of VARIVAX to children and adolescents. (5.6, 7.1)

---- ADVERSE REACTIONS ---

- Frequently reported (≥10%) adverse reactions in children ages 1 to 12 years include:
 - o fever ≥102.0°F (38.9°C) oral: 14.7%
 - o injection-site complaints: 19.3% (6.1)
- Frequently reported (≥10%) adverse reactions in adolescents and adults ages 13 years and older include:
 - o fever ≥100.0°F (37.8°C) oral: 10.2%
 - o injection-site complaints: 24.4% (6.1)
- Other reported adverse reactions in all age groups include:
 - o varicella-like rash (injection site)
 - o varicella-like rash (generalized) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

--- DRUG INTERACTIONS ---

- Reye syndrome has been reported in children and adolescents following the use of salicylates during wild-type varicella infection. (5.6, 7.1)
- Passively acquired antibodies from blood, plasma, or immunoglobulin potentially may inhibit the response to varicella vaccination. (5.5, 7.2)
- Tuberculin skin testing may be performed before VARIVAX is administered or on the same day, or six weeks following vaccination with VARIVAX. (7.3)

----- USE IN SPECIFIC POPULATIONS -----

Pregnancy: Do not administer VARIVAX to females who are pregnant. Pregnancy should be avoided for 3 months following vaccination with VARIVAX. (4.4, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VARIVAX® is a vaccine indicated for active immunization for the prevention of varicella in individuals 12 months of age and older.

2 DOSAGE AND ADMINISTRATION

Subcutaneous administration only

2.1 Recommended Dose and Schedule

VARIVAX is administered as an approximately 0.5-mL dose by subcutaneous injection into the outer aspect of the upper arm (deltoid region) or the anterolateral thigh.

Do not administer this product intravascularly or intramuscularly.

Children (12 months to 12 years of age)

If a second dose is administered, there should be a minimum interval of 3 months between doses [see Clinical Studies (14.1)].

Adolescents (≥13 years of age) and Adults

Two doses of vaccine, to be administered with a minimum interval of 4 weeks between doses [see Clinical Studies (14.1)].

2.2 Reconstitution Instructions

When reconstituting the vaccine, use only the sterile diluent supplied with VARIVAX. The sterile diluent does not contain preservatives or other anti-viral substances which might inactivate the vaccine virus.

Use a sterile syringe free of preservatives, antiseptics, and detergents for each reconstitution and injection of VARIVAX because these substances may inactivate the vaccine virus.

To reconstitute the vaccine, first withdraw the total volume of provided sterile diluent into a syringe. Inject all of the withdrawn diluent into the vial of lyophilized vaccine and gently agitate to mix thoroughly. Withdraw the entire contents into the syringe and inject the total volume (approximately 0.5 mL) of reconstituted vaccine subcutaneously. VARIVAX, when reconstituted, is a clear, colorless to pale yellow liquid.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored.

To minimize loss of potency, administer VARIVAX immediately after reconstitution. Discard if reconstituted vaccine is not used within 30 minutes.

Do not freeze reconstituted vaccine.

Do not combine VARIVAX with any other vaccine through reconstitution or mixing.

3 DOSAGE FORMS AND STRENGTHS

VARIVAX is a suspension for injection supplied as a single-dose vial of lyophilized vaccine to be reconstituted using the accompanying sterile diluent [see Dosage and Administration (2.2) and How Supplied/Storage and Handling (16)]. A single dose after reconstitution is approximately 0.5 mL.

4 CONTRAINDICATIONS

4.1 Severe Allergic Reaction

Do not administer VARIVAX to individuals with a history of anaphylactic or severe allergic reaction to any component of the vaccine (including neomycin and gelatin) or to a previous dose of a varicella-containing vaccine.

4.2 Immunosuppression

Do not administer VARIVAX to immunosuppressed or immunodeficient individuals, including those with a history of primary or acquired immunodeficiency states, leukemia, lymphoma or other malignant

neoplasms affecting the bone marrow or lymphatic system, AIDS, or other clinical manifestations of infection with human immunodeficiency virus (HIV).

Do not administer VARIVAX to individuals receiving immunosuppressive therapy, including individuals receiving immunosuppressive doses of corticosteroids.

VARIVAX is a live, attenuated varicella-zoster vaccine (VZV) and may cause an extensive vaccine-associated rash or disseminated disease in individuals who are immunosuppressed or immunodeficient.

4.3 Concurrent Illness

Do not administer VARIVAX to individuals with any febrile illness. Do not administer VARIVAX to individuals with active, untreated tuberculosis.

4.4 Pregnancy

Do not administer VARIVAX to individuals who are pregnant because the effects of the vaccine on fetal development are unknown. Wild-type varicella (natural infection) is known to sometimes cause fetal harm. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following vaccination [see Use in Specific Populations (8.1) and Patient Counseling Information (17)].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Allergic Reactions

Adequate treatment provisions, including epinephrine injection (1:1000), should be available for immediate use should anaphylaxis occur.

5.2 Family History of Immunodeficiency

Vaccination should be deferred in patients with a family history of congenital or hereditary immunodeficiency until the patient's immune status has been evaluated and the patient has been found to be immunocompetent.

5.3 Use in HIV-Infected Individuals

The Advisory Committee for Immunization Practices (ACIP) has recommendations on the use of varicella vaccine in HIV-infected individuals.

5.4 Risk of Vaccine Virus Transmission

Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from a mother who did not develop a varicella-like rash to her newborn infant has been reported.

Due to the concern for transmission of vaccine virus, vaccine recipients should attempt to avoid whenever possible close association with susceptible high-risk individuals for up to six weeks following vaccination with VARIVAX. Susceptible high-risk individuals include:

- Immunocompromised individuals;
- Pregnant women without documented history of varicella or laboratory evidence of prior infection;
- Newborn infants of mothers without documented history of varicella or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

5.5 Immune Globulins and Transfusions

Immunoglobulins should not be given concomitantly with VARIVAX. Vaccination should be deferred for at least 5 months following blood or plasma transfusions, or administration of immune globulin(s) {1}.

Following administration of VARIVAX, immune globulin(s) should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination {1}. [See Drug Interactions (7.2).]

5.6 Salicylate Therapy

Avoid use of salicylates (aspirin) or salicylate-containing products in children and adolescents 12 months through 17 years of age for six weeks following vaccination with VARIVAX because of the association of Reye syndrome with aspirin therapy and wild-type varicella infection. [See Drug Interactions (7.1).]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in clinical practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

In clinical trials {2-9}, VARIVAX was administered to over 11,000 healthy children, adolescents, and adults.

In a double-blind, placebo-controlled study among 914 healthy children and adolescents who were serologically confirmed to be susceptible to varicella, the only adverse reactions that occurred at a significantly (p<0.05) greater rate in vaccine recipients than in placebo recipients were pain and redness at the injection site {2}.

Children 1 to 12 Years of Age

One-Dose Regimen in Children

In clinical trials involving healthy children monitored for up to 42 days after a single dose of VARIVAX, the frequency of fever, injection-site complaints, or rashes were reported as shown in Table 1:

Table 1: Fever, Local Reactions, and Rashes (%) in Children 1 to 12 Years of Age 0 to 42

Days After Receipt of a Single Dose of VARIVAX

| Buys Aitor Recorpt of a onight Book of VARIVAR | | | | | | |
|--|------|-------------------------------|---|--|--|--|
| Reaction | N | % Experiencing Reaction | Peak Occurrence During Postvaccination Days | | | |
| Fever ≥102.0°F (38.9°C) Oral | 8827 | 14.7% | 0 to 42 | | | |
| Injection-site complaints (pain/soreness, swelling and/or erythema, rash, pruritus, hematoma, induration, stiffness) | 8916 | 19.3% | 0 to 2 | | | |
| Varicella-like rash (injection site) Median number of lesions | 8916 | 3.4% | 8 to 19 | | | |
| Varicella-like rash (generalized) | 8916 | 3.8% | 5 to 26 | | | |
| Median number of lesions | | 5 | | | | |

In addition, adverse events occurring at a rate of ≥1% are listed in decreasing order of frequency: upper respiratory illness, cough, irritability/nervousness, fatigue, disturbed sleep, diarrhea, loss of appetite, vomiting, otitis, diaper rash/contact rash, headache, teething, malaise, abdominal pain, other rash, nausea, eye complaints, chills, lymphadenopathy, myalgia, lower respiratory illness, allergic reactions (including allergic rash, hives), stiff neck, heat rash/prickly heat, arthralgia, eczema/dry skin/dermatitis, constipation, itching.

Pneumonitis has been reported rarely (<1%) in children vaccinated with VARIVAX.

Febrile seizures have occurred at a rate of <0.1% in children vaccinated with VARIVAX.

Two-Dose Regimen in Children

Nine hundred eighty-one (981) subjects in a clinical trial received 2 doses of VARIVAX 3 months apart and were actively followed for 42 days after each dose. The 2-dose regimen of varicella vaccine had a safety profile comparable to that of the 1-dose regimen. The overall incidence of injection-site clinical complaints (primarily erythema and swelling) observed in the first 4 days following vaccination was 25.4% Postdose 2 and 21.7% Postdose 1, whereas the overall incidence of systemic clinical complaints in the 42-day follow-up period was lower Postdose 2 (66.3%) than Postdose 1 (85.8%).

Adolescents (13 Years of Age and Older) and Adults

In clinical trials involving healthy adolescents and adults, the majority of whom received two doses of VARIVAX and were monitored for up to 42 days after any dose, the frequencies of fever, injection-site complaints, or rashes are shown in Table 2.

Table 2: Fever, Local Reactions, and Rashes (%) in Adolescents and Adults 0 to 42 Days After Receipt of VARIVAX

| Reaction | N | % Post Dose 1 | Peak Occurrence in Postvaccination Days | N | % Post Dose 2 | Peak Occurrence in Postvaccination Days |
|---|------|------------------|--|-----|------------------|--|
| Fever ≥100.0°F (37.8°C) Oral | 1584 | 10.2% | 14 to 27 | 956 | 9.5% | 0 to 42 |
| Injection-site complaints (soreness, erythema, swelling, rash, pruritus, pyrexia, hematoma, induration, numbness) | 1606 | 24.4% | 0 to 2 | 955 | 32.5% | 0 to 2 |
| Varicella-like rash (injection site) Median number of lesions | 1606 | 3% 2 | 6 to 20 | 955 | 1% 2 | 0 to 6 |
| Varicella-like rash (generalized) | 1606 | 5.5% | 7 to 21 | 955 | 0.9% | 0 to 23 |
| Median number of lesions | | 5 | | | 5.5 | |

In addition, adverse events reported at a rate of ≥1% are listed in decreasing order of frequency: upper respiratory illness, headache, fatigue, cough, myalgia, disturbed sleep, nausea, malaise, diarrhea, stiff neck, irritability/nervousness, lymphadenopathy, chills, eye complaints, abdominal pain, loss of appetite, arthralgia, otitis, itching, vomiting, other rashes, constipation, lower respiratory illness, allergic reactions (including allergic rash, hives), contact rash, cold/canker sore.

6.2 Post-Marketing Experience

Broad use of VARIVAX could reveal adverse events not observed in clinical trials.

The following additional adverse events, regardless of causality, have been reported during post-marketing use of VARIVAX:

Body as a Whole

Anaphylaxis (including anaphylactic shock) and related phenomena such as angioneurotic edema, facial edema, and peripheral edema.

Eye Disorders

Necrotizing retinitis (in immunocompromised individuals).

Hemic and Lymphatic System

Aplastic anemia; thrombocytopenia (including idiopathic thrombocytopenic purpura (ITP)).

Infections and Infestations

Varicella (vaccine strain).

Nervous/Psychiatric

Encephalitis; cerebrovascular accident; transverse myelitis; Guillain-Barré syndrome; Bell's palsy; ataxia; non-febrile seizures; aseptic meningitis; meningitis; dizziness; paresthesia.

Cases of encephalitis or meningitis caused by vaccine strain varicella virus have been reported in immunocompetent individuals previously vaccinated with VARIVAX months to years after vaccination. Reported cases were commonly associated with preceding or concurrent herpes zoster rash. [See Clinical Pharmacology (12.2)].

Respiratory

Pharyngitis; pneumonia/pneumonitis.

Skin

Stevens-Johnson syndrome; erythema multiforme; Henoch-Schönlein purpura; secondary bacterial infections of skin and soft tissue, including impetigo and cellulitis; herpes zoster.

7 DRUG INTERACTIONS

7.1 Salicylates

No cases of Reye syndrome have been observed following vaccination with VARIVAX. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with VARIVAX, as Reye syndrome has been reported following the use of salicylates during wild-type varicella infection [see Warnings and Precautions (5.6)].

7.2 Immune Globulins and Transfusions

Blood, plasma, and immune globulins contain antibodies that may interfere with vaccine virus replication and decrease the immune response to VARIVAX. Vaccination should be deferred for at least 5 months following blood or plasma transfusions, or administration of immune globulin(s) {1}.

Following administration of VARIVAX, immune globulin(s) should not be given for 2 months thereafter unless its use outweighs the benefits of vaccination {1}. [See Warnings and Precautions (5.5).]

7.3 Tuberculin Skin Testing

Tuberculin skin testing, with tuberculin purified protein derivative (PPD), may be performed before VARIVAX is administered or on the same day, or at least 4 weeks following vaccination with VARIVAX, as other live virus vaccines may cause a temporary depression of tuberculin skin test sensitivity leading to false negative results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

VARIVAX is contraindicated for use in pregnant women because the vaccine contains live, attenuated varicella virus, and it is known that wild-type varicella virus, if acquired during pregnancy, can cause congenital varicella syndrome [see Contraindications (4.4) and Patient Counseling Information (17)]. No increased risk for miscarriage, major birth defect or congenital varicella syndrome was observed in a pregnancy exposure registry that monitored outcomes after inadvertent use. There are no relevant animal data.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively.

A pregnancy exposure registry was maintained from 1995 to 2013 to monitor pregnancy and fetal outcomes following inadvertent administration of VARIVAX. The registry prospectively enrolled 1522 women who received a dose of VARIVAX during pregnancy or within three months prior to conception. After excluding elective terminations (n=60), ectopic pregnancies (n=1) and those lost to follow-up (n=556), there were 905 pregnancies with known outcomes. Of these 905 pregnancies, 271 (30%) were in women who were vaccinated within the three months prior to conception. Miscarriage was reported for 10% of pregnancies (95/905), and major birth defects were reported for 2.6% of live born infants (21/819). These rates of assessed outcomes were consistent with estimated background rates. None of the women who received VARIVAX vaccine delivered infants with abnormalities consistent with congenital varicella syndrome.

8.2 Lactation

Risk Summary

It is not known whether varicella vaccine virus is excreted in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VARIVAX, and any potential adverse effects on the breastfed child from VARIVAX or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

No clinical data are available on safety or efficacy of VARIVAX in children less than 12 months of age.

8.5 Geriatric Use

Clinical studies of VARIVAX did not include sufficient numbers of seronegative subjects aged 65 and over to determine whether they respond differently from younger subjects.

11 DESCRIPTION

VARIVAX [Varicella Virus Vaccine Live] is a preparation of the Oka/Merck strain of live, attenuated varicella virus. The virus was initially obtained from a child with wild-type varicella, then introduced into human embryonic lung cell cultures, adapted to and propagated in embryonic guinea pig cell cultures and finally propagated in human diploid cell cultures (WI-38). Further passage of the virus for varicella vaccine was performed at Merck Research Laboratories (MRL) in human diploid cell cultures (MRC-5) that were

free of adventitious agents. This live, attenuated varicella vaccine is a lyophilized preparation containing sucrose, phosphate, glutamate, and processed gelatin as stabilizers.

VARIVAX, when reconstituted as directed, is a sterile preparation for subcutaneous injection. Each approximately 0.5-mL dose contains a minimum of 1350 plaque-forming units (PFU) of Oka/Merck varicella virus when reconstituted and stored at room temperature for a maximum of 30 minutes. Each 0.5-mL dose also contains approximately 25 mg of sucrose, 12.5 mg hydrolyzed gelatin, 3.2 mg of sodium chloride, 0.5 mg of monosodium L-glutamate, 0.45 mg of sodium phosphate dibasic, 0.08 mg of potassium phosphate monobasic, and 0.08 mg of potassium chloride. The product also contains residual components of MRC-5 cells including DNA and protein and trace quantities of sodium phosphate monobasic, EDTA, neomycin and fetal bovine serum. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VARIVAX induces both cell-mediated and humoral immune responses to varicella-zoster virus. The relative contributions of humoral immunity and cell-mediated immunity to protection from varicella are unknown.

12.2 Pharmacodynamics

Transmission

In the placebo-controlled efficacy trial, transmission of vaccine virus was assessed in household settings (during the 8-week postvaccination period) in 416 susceptible placebo recipients who were household contacts of 445 vaccine recipients. Of the 416 placebo recipients, three developed varicella and seroconverted, nine reported a varicella-like rash and did not seroconvert, and six had no rash but seroconverted. If vaccine virus transmission occurred, it did so at a very low rate and possibly without recognizable clinical disease in contacts. These cases may represent either wild-type varicella from community contacts or a low incidence of transmission of vaccine virus from vaccinated contacts [see Warnings and Precautions (5.4)] {2,12}. Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from a mother who did not develop a varicella-like rash to her newborn infant has also been reported.

Herpes Zoster

Overall, 9454 healthy children (12 months to 12 years of age) and 1648 adolescents and adults (13 years of age and older) have been vaccinated with VARIVAX in clinical trials. Eight cases of herpes zoster have been reported in children during 42,556 person-years of follow-up in clinical trials, resulting in a calculated incidence of at least 18.8 cases per 100,000 person-years. The completeness of this reporting has not been determined. One case of herpes zoster has been reported in the adolescent and adult age group during 5410 person-years of follow-up in clinical trials, resulting in a calculated incidence of 18.5 cases per 100,000 person-years. All 9 cases were mild and without sequelae. Two cultures (one child and one adult) obtained from vesicles were positive for wild-type VZV as confirmed by restriction endonuclease analysis {13}. The long-term effect of VARIVAX on the incidence of herpes zoster, particularly in those vaccinees exposed to wild-type varicella, is unknown at present.

In children, the reported rate of herpes zoster in vaccine recipients appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella {14}. The incidence of herpes zoster in adults who have had wild-type varicella infection is higher than that in children.

The vaccine virus (Oka/Merck strain) contained in VARIVAX may establish latency of varicella zoster virus in immunocompetent individuals, with the potential for later development of herpes zoster [see Adverse Reactions (6.2)].

12.6 Duration of Protection

The duration of protection of VARIVAX is unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination {15} [see Clinical Studies (14.1)]. A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella which could account for the apparent long-term protection after vaccination in these studies.

14 CLINICAL STUDIES

14.1 Clinical Efficacy

The protective efficacy of VARIVAX was established by: (1) a placebo-controlled, double-blind clinical trial, (2) comparing varicella rates in vaccinees versus historical controls, and (3) assessing protection from disease following household exposure.

Clinical Data in Children

One-Dose Regimen in Children

Although no placebo-controlled trial was carried out with VARIVAX using the current vaccine, a placebo-controlled trial was conducted using a formulation containing 17,000 PFU per dose {2,16}. In this trial, a single dose of VARIVAX protected 96 to 100% of children against varicella over a two-year period. The study enrolled healthy individuals 1 to 14 years of age (n=491 vaccine, n=465 placebo). In the first year, 8.5% of placebo recipients contracted varicella, while no vaccine recipient did, for a calculated protection rate of 100% during the first varicella season. In the second year, when only a subset of individuals agreed to remain in the blinded study (n=163 vaccine, n=161 placebo), 96% protective efficacy was calculated for the vaccine group as compared to placebo.

In early clinical trials, a total of 4240 children 1 to 12 years of age received 1000 to 1625 PFU of attenuated virus per dose of VARIVAX and have been followed for up to nine years post single-dose vaccination. In this group there was considerable variation in varicella rates among studies and study sites, and much of the reported data were acquired by passive follow-up. It was observed that 0.3 to 3.8% of vaccinees per year reported varicella (called breakthrough cases). This represents an approximate 83% (95% confidence interval [CI], 82%, 84%) decrease from the age-adjusted expected incidence rates in susceptible subjects over this same period {14}. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease (median of the maximum number of lesions <50). In one study, a total of 47% (27/58) of breakthrough cases had <50 lesions compared with 8% (7/92) in unvaccinated individuals, and 7% (4/58) of breakthrough cases had >300 lesions compared with 50% (46/92) in unvaccinated individuals {17}.

Among a subset of vaccinees who were actively followed in these early trials for up to nine years postvaccination, 179 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 84% (150/179) of exposed children, while 16% (29/179) reported a mild form of varicella (38% [11/29] of the cases with a maximum total number of <50 lesions; no individuals with >300 lesions). This represents an 81% reduction in the expected number of varicella cases utilizing the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

In later clinical trials, a total of 1114 children 1 to 12 years of age received 2900 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to 10 years post single-dose vaccination. It was observed that 0.2% to 2.3% of vaccinees per year reported breakthrough varicella for up to 10 years post single-dose vaccination. This represents an estimated efficacy of 94% (95% CI, 93%, 96%), compared with the age-adjusted expected incidence rates in susceptible subjects over the same period {2,14,18}. In those who developed breakthrough varicella postvaccination, the majority experienced mild disease, with the median of the maximum total number of lesions <50. The severity of reported breakthrough varicella, as measured by number of lesions and maximum temperature, appeared not to increase with time since vaccination.

Among a subset of vaccinees who were actively followed in these later trials for up to 10 years postvaccination, 95 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella in 92% (87/95) of exposed children, while 8% (8/95) reported a mild form of varicella (maximum total number of lesions <50; observed range, 10 to 34). This represents an estimated efficacy of 90% (95% CI, 82%, 96%) based on the historical attack rate of 87% following household exposure to varicella in unvaccinated individuals in the calculation of efficacy.

Two-Dose Regimen in Children

In a clinical trial, a total of 2216 children 12 months to 12 years of age with a negative history of varicella were randomized to receive either 1 dose of VARIVAX (n=1114) or 2 doses of VARIVAX (n=1102) given 3 months apart. Subjects were actively followed for varicella, any varicella-like illness, or herpes zoster and any exposures to varicella or herpes zoster on an annual basis for 10 years after

vaccination. Persistence of VZV antibody was measured annually for 9 years. Most cases of varicella reported in recipients of 1 dose or 2 doses of vaccine were mild {15}. The estimated vaccine efficacy for the 10-year observation period was 94% for 1 dose and 98% for 2 doses (p<0.001). This translates to a 3.4-fold lower risk of developing varicella >42 days postvaccination during the 10-year observation period in children who received 2 doses than in those who received 1 dose (2.2% vs. 7.5%, respectively).

Clinical Data in Adolescents and Adults

Two-Dose Regimen in Adolescents and Adults

In early clinical trials, a total of 796 adolescents and adults received 905 to 1230 PFU of attenuated virus per dose of VARIVAX and have been followed for up to six years following 2-dose vaccination. A total of 50 clinical varicella cases were reported >42 days following 2-dose vaccination. Based on passive follow-up, the annual varicella breakthrough event rate ranged from <0.1 to 1.9%. The median of the maximum total number of lesions ranged from 15 to 42 per year.

Although no placebo-controlled trial was carried out in adolescents and adults, the protective efficacy of VARIVAX was determined by evaluation of protection when vaccinees received 2 doses of VARIVAX 4 or 8 weeks apart and were subsequently exposed to varicella in a household setting. Among the subset of vaccinees who were actively followed in these early trials for up to six years, 76 individuals had household exposure to varicella. There were no reports of breakthrough varicella in 83% (63/76) of exposed vaccinees, while 17% (13/76) reported a mild form of varicella. Among 13 vaccinated individuals who developed breakthrough varicella after a household exposure, 62% (8/13) of the cases reported maximum total number of lesions <50, while no individual reported >75 lesions. The attack rate of unvaccinated adults exposed to a single contact in a household has not been previously studied. Utilizing the previously reported historical attack rate of 87% for wild-type varicella following household exposure to varicella among unvaccinated children in the calculation of efficacy, this represents an approximate 80% reduction in the expected number of cases in the household setting.

In later clinical trials, a total of 220 adolescents and adults received 3315 to 9000 PFU of attenuated virus per dose of VARIVAX and have been actively followed for up to six years following 2-dose vaccination. A total of 3 clinical varicella cases were reported >42 days following 2-dose vaccination. Two cases reported <50 lesions and none reported >75. The annual varicella breakthrough event rate ranged from 0 to 1.2%. Among the subset of vaccinees who were actively followed in these later trials for up to five years, 16 individuals were exposed to an unvaccinated individual with wild-type varicella in a household setting. There were no reports of breakthrough varicella among the exposed vaccinees.

There are insufficient data to assess the rate of protective efficacy of VARIVAX against the serious complications of varicella in adults (e.g., encephalitis, hepatitis, pneumonitis) and during pregnancy (congenital varicella syndrome).

14.2 Immunogenicity

In clinical trials, varicella antibodies have been evaluated following vaccination with formulations of VARIVAX containing attenuated virus ranging from 1000 to 50,000 PFU per dose in healthy individuals ranging from 12 months to 55 years of age {2,9}.

One-Dose Regimen in Children

In prelicensure efficacy studies, seroconversion was observed in 97% of vaccinees at approximately 4 to 6 weeks postvaccination in 6889 susceptible children 12 months to 12 years of age. Titers ≥5 gpELISA units/mL were induced in approximately 76% of children vaccinated with a single dose of vaccine at 1000 to 17,000 PFU per dose. Rates of breakthrough disease were significantly lower among children with VZV antibody titers ≥5 gpELISA units/mL compared with children with titers <5 gpELISA units/mL.

Two-Dose Regimen in Children

In a multicenter study, 2216 healthy children 12 months to 12 years of age received either 1 dose of VARIVAX or 2 doses administered 3 months apart. The immunogenicity results are shown in Table 3.

Table 3: Summary of VZV Antibody Responses at 6 Weeks Postdose 1 and 6 Weeks Postdose 2 in Initially Seronegative Children 12 Months to 12 Years of Age (Vaccinations 3 Months Apart)

| VARIVAX | VARIVAX 2-Dose Regimen (3 months apart) (N=1102) | | |
|-----------------|--|------------------|--|
| 1-Dose Regimen | | | |
| (N=1114) | | | |
| 6 Weeks | 6 Weeks Postdose | 6 Weeks Postdose | |
| Postvaccination | 1 (n=851) | 2 (n=769) | |
| (n=892) | | | |

| Seroconversion Rate | 98.9% | 99.5% | 99.9% |
|---------------------------|--------------|--------------|----------------|
| Percent with VZV Antibody | 84.9% | 87.3% | 99.5% |
| Titer ≥5 gpELISA units/mL | | | |
| Geometric mean titers in | 12.0 | 12.8 | 141.5 |
| gpELISA units/mL (95% CI) | (11.2, 12.8) | (11.9, 13.7) | (132.3, 151.3) |

N = Number of subjects vaccinated.

The results from this study and other studies in which a second dose of VARIVAX was administered 3 to 6 years after the initial dose demonstrate significant boosting of the VZV antibodies with a second dose. VZV antibody levels after 2 doses given 3 to 6 years apart are comparable to those obtained when the 2 doses are given 3 months apart.

Two-Dose Regimen in Adolescents and Adults

In a multicenter study involving susceptible adolescents and adults 13 years of age and older, 2 doses of VARIVAX administered 4 to 8 weeks apart induced a seroconversion rate of approximately 75% in 539 individuals 4 weeks after the first dose and of 99% in 479 individuals 4 weeks after the second dose. The average antibody response in vaccinees who received the second dose 8 weeks after the first dose was higher than that in vaccinees who received the second dose 4 weeks after the first dose. In another multicenter study involving adolescents and adults, 2 doses of VARIVAX administered 8 weeks apart induced a seroconversion rate of 94% in 142 individuals 6 weeks after the first dose and 99% in 122 individuals 6 weeks after the second dose.

14.3 Persistence of Immune Response

One-Dose Regimen in Children

In clinical studies involving healthy children who received 1 dose of vaccine, detectable VZV antibodies were present in 99.0% (3886/3926) at 1 year, 99.3% (1555/1566) at 2 years, 98.6% (1106/1122) at 3 years, 99.4% (1168/1175) at 4 years, 99.2% (737/743) at 5 years, 100% (142/142) at 6 years, 97.4% (38/39) at 7 years, 100% (34/34) at 8 years, and 100% (16/16) at 10 years postvaccination. Two-Dose Regimen in Children

In recipients of 1 dose of VARIVAX over 9 years of follow-up, the geometric mean titers (GMTs) and the percent of subjects with VZV antibody titers ≥5 gpELISA units/mL generally increased. The GMTs and percent of subjects with VZV antibody titers ≥5 gpELISA units/mL in the 2-dose recipients were higher than those in the 1-dose recipients for the first year of follow-up and generally comparable thereafter. The cumulative rate of VZV antibody persistence with both regimens remained very high at year 9 (99.0% for the 1-dose group and 98.8% for the 2-dose group).

Two-Dose Regimen in Adolescents and Adults

In clinical studies involving healthy adolescents and adults who received 2 doses of vaccine, detectable VZV antibodies were present in 97.9% (568/580) at 1 year, 97.1% (34/35) at 2 years, 100% (144/144) at 3 years, 97.0% (98/101) at 4 years, 97.4% (76/78) at 5 years, and 100% (34/34) at 6 years postvaccination.

A boost in antibody levels has been observed in vaccinees following exposure to wild-type varicella, which could account for the apparent long-term persistence of antibody levels in these studies.

14.4 Studies with Other Vaccines

Concomitant Administration with M-M-R II

In combined clinical studies involving 1080 children 12 to 36 months of age, 653 received VARIVAX and M-M-R II concomitantly at separate injection sites and 427 received the vaccines six weeks apart. Seroconversion rates and antibody levels to measles, mumps, rubella, and varicella were comparable between the two groups at approximately six weeks postvaccination.

<u>Concomitant Administration with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine</u> Adsorbed (DTaP) and Oral Poliovirus Vaccine (OPV)

In a clinical study involving 318 children 12 months to 42 months of age, 160 received an investigational varicella-containing vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with booster doses of DTaP and OPV (no longer licensed in the United States). The comparator group of 144 children received M-M-R II concomitantly with booster doses of DTaP and OPV followed by VARIVAX six weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV and the percentage of vaccinees whose titers were boosted for diphtheria, tetanus, pertussis, and polio were comparable between the two groups.

n = Number of subjects included in immunogenicity analysis.

Anti-VZV levels were decreased when the investigational vaccine containing varicella was administered concomitantly with DTaP {19}. No clinically significant differences were noted in adverse reactions between the two groups.

Concomitant Administration with PedvaxHIB®

In a clinical study involving 307 children 12 to 18 months of age, 150 received an investigational varicella-containing vaccine (a formulation combining measles, mumps, rubella, and varicella in one syringe) concomitantly with a booster dose of PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], while 130 received M-M-R II concomitantly with a booster dose of PedvaxHIB followed by VARIVAX 6 weeks later. At six weeks postvaccination, seroconversion rates for measles, mumps, rubella, and VZV, and GMTs for PedvaxHIB were comparable between the two groups. Anti-VZV levels were decreased when the investigational vaccine containing varicella was administered concomitantly with PedvaxHIB {20}. No clinically significant differences in adverse reactions were seen between the two groups.

Concomitant Administration with M-M-R II and COMVAX

In a clinical study involving 822 children 12 to 15 months of age, 410 received COMVAX, M-M-R II, and VARIVAX concomitantly at separate injection sites, and 412 received COMVAX followed by M-M-R II and VARIVAX given concomitantly at separate injection sites, 6 weeks later. At 6 weeks postvaccination, the immune responses for the subjects who received the concomitant doses of COMVAX, M-M-R II, and VARIVAX were similar to those of the subjects who received COMVAX followed 6 weeks later by M-M-R II and VARIVAX with respect to all antigens administered. There were no clinically important differences in reaction rates when the three vaccines were administered concomitantly versus six weeks apart.

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16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4827/4309 —VARIVAX is supplied as follows:

- (1) a box of 10 single-dose vials of lyophilized vaccine (package A), NDC 0006-4827-00
- (2) a box of 10 vials of diluent (package B).

Storage

Vaccine Vial

During shipment, maintain the vaccine at a temperature between $-58^{\circ}F$ and $+5^{\circ}F$ ($-50^{\circ}C$ and $-15^{\circ}C$). Use of dry ice may subject VARIVAX to temperatures colder than $-58^{\circ}F$ ($-50^{\circ}C$).

Before reconstitution, store the lyophilized vaccine in a freezer at a temperature between -58°F and +5°F (-50°C and -15°C). Any freezer (e.g., chest, frost-free) that reliably maintains a temperature between -58°F and +5°F (-50°C and -15°C) and has a separate sealed freezer door is acceptable for storing VARIVAX. Routine defrost cycling of a frost-free freezer is acceptable.

VARIVAX may be stored at refrigerator temperature (36°F to 46°F, 2°C to 8°C) for up to 72 continuous hours prior to reconstitution. Vaccine stored at 2°C to 8°C which is not used within 72 hours of removal from +5°F (-15°C) storage should be discarded.

Before reconstitution, protect from light.

DISCARD IF RECONSTITUTED VACCINE IS NOT USED WITHIN 30 MINUTES.

Diluent Vial

The vial of diluent should be stored separately at room temperature (68°F to 77°F, 20°C to 25°C), or in the refrigerator.

For information regarding the product or questions regarding storage conditions, call 1-800-9-VARIVAX (1-800-982-7482).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Discuss the following with the patient:

- Question the patient, parent, or guardian about reactions to previous vaccines.
- Provide a copy of the patient information (PPI) located at the end of this insert and discuss any questions or concerns.

- Inform patient, parent, or guardian that vaccination with VARIVAX may not result in protection of all healthy, susceptible children, adolescents, and adults.
- Inform female patients to avoid pregnancy for three months following vaccination.
- Inform patient, parent, or guardian of the benefits and risks of VARIVAX.
- Instruct patient, parent, or guardian to report any adverse reactions or any symptoms of concern to their healthcare professional.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at http://www.vaers.hhs.gov.

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LIVE ATTENUATED VARICELLA VIRUS VACCINE

Efficacy Trial in Healthy Children

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Abstract We conducted a double-blind, placebo-controlled efficacy trial of the live attenuated Oka/Merck varicella vaccine among 956 children between the ages of 1 and 14 years, with a negative clinical history of varicella. Of the 914 children who were serologically confirmed to be susceptible to varicella, 468 received vaccine and 446 received placebo. The vaccine produced few clinical reactions and was well tolerated. There was no clinical evidence of viral spread from vaccinated children to sibling controls. Approximately eight weeks after vaccination, 94

VARICELLA (chickenpox) is a highly contagious disease of human beings that is caused by *Herpesvirus varicellae*, or varicella-zoster virus. Chickenpox usually occurs as a mild childhood disease but can cause severe or even fatal illness. Li is estimated that over 90 per cent of adults in the United States have serologic evidence of past varicella infection. Immunity after the disease can be long term or permanent. Zoster may result from activation of latent varicella-zoster virus during a period of waning immunity.

Since the 19th century the potential severity of chickenpox has stimulated interest in its prevention by vaccination. Experimental live virus vaccines have advanced from the early use of vesicular fluid to attenuated cell-free virus grown in tissue cultures.⁶⁻⁹

In 1974 Takahashi et al. developed the first live attenuated varicella virus vaccine from the Oka strain. Other varicella vaccines have been tested in limited populations. He Oka strain has been most widely tested and is reported to be safe and highly immunogenic when administered to healthy adults and children as well as to patients with leukemia and to other immunosuppressed persons. Other limited persons with leukemia and to other immunosuppressed persons.

per cent of the initially seronegative children who received vaccine had detectable antibody to varicella. During the nine-month surveillance period, 39 clinically diagnosed cases of varicella, 38 of which were confirmed by laboratory tests, occurred among study participants. All 39 cases occurred in placebo recipients; no child who received vaccine contracted varicella. The vaccine was 100 per cent efficacious in preventing varicella in this population of healthy children (P<10⁻⁹). (N Engl J Med 1984; 310:1409-15.)

exposure. 10,14-16 However, it has not yet been shown to be efficacious in protecting against natural disease when administered to healthy children before exposure. This paper reports the results of a large, double-blind, randomized, placebo-controlled trial to determine the efficacy of the Oka-strain varicella virus vaccine in healthy children.

METHODS

The varicella vaccine and placebo used in this trial were prepared by Merck Sharp & Dohme Research Laboratories, West Point, Pa. The vaccine (Lot 867/C-H198) was prepared from seed stock obtained from Dr. Takahashi at the 24th passage. It had been passed 11 times in human embryonic lung fibroblasts, 12 times in guinea pig embryonic cell culture, and once in human diploid fibroblasts (WI-38). At the Merck Sharp & Dohme laboratory the virus was passed six additional times in human diploid fibroblast (MRC-5) cells, for a total of 30 passages. Infected cell sheets were rinsed; mechanically detached with glass beads from the vessel surface into sucrose, phosphate, glutamate, and human serum albumin stabilizer; pooled; sampled for preliminary infectivity titers and microbial sterility; and stored at -70°C. When the sterility and infectivity tests were satisfactorily completed, the bulk pools were thawed, combined, and sonicated to disrupt the cells. The clarified bulk vaccine was tested for safety, placed in glass vials, lyophilized, and stored at -20°C. The final container vaccine was tested for sterility, neomycin concentration (45 mg per milliliter), isotonicity, and safety in cultures, mice, and guinea pigs, and was reidentified by the plaque-reduction assay, using human pre- and post-varicella serum and equine hyperimmune serum. The vaccine met all safety standards set for other live virus vaccines by the Food and Drug Administration.20 The infectivity titer of the vaccine was 8700 plaque-forming units per milliliter.

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the vaccine in both lyophilized and reconstituted forms but contained no viral material. The placebo consisted of lyophilized stabilizer containing approximately 45 mg of neomycin per milliliter. The final container was tested for sterility, isotonicity, and safety in the same manner as the vaccine and was identified as nonreactive to positive varicella antiserum. Both vaccine and placebo were reconstituted with 1.2 ml of sterile distilled water free of preservatives, and 1.0 ml was administered subcutaneously.

Enrollment

This clinical trial was conducted with the approval of the Committee on Studies Involving Human Beings, University of Pennsylvania. Written consent was obtained from a parent of each child in the study.

Children recruited for the study were from middle-class suburban Philadelphia, primarily from nine private pediatric practices. A small number of children were enrolled from two parochial schools and one day-care center in the area. Recruitment efforts were concentrated on families in which there were two or more children who met all the eligibility criteria. Children entering this trial had to meet all the following criteria: between 1 and 14 years of age, good health, no history of cancer or immune deficiency, no clinical history of varicella, no exposure to varicella within the previous four weeks, no live virus or pertussis vaccinations within the previous four weeks, no known sensitivity to neomycin, and no children in the family for whom exposure to varicella could be judged a special risk (e.g., siblings with neoplastic disease or immune deficiency).

Randomization

Randomization was done by the vaccine manufacturer using a computer random-number generator. Within each family, study participants were randomly assigned by code to receive either vaccine or placebo, on the basis of family size. Among families with an even number of participants, half received vaccine and half received placebo. Among families with an odd number of participants, about half had an excess of vaccine recipients and about half had an excess of placebo recipients. The study physician, nurses, participants, and parents remained blinded throughout the course of the study.

Clinical Follow-up

A parent or guardian of each child in the study was asked to take the child's temperature daily for the eight-week period after administration of vaccine or placebo and to document on a Vaccination Report Card any clinical symptoms during this period. In addition to daily temperatures, the parent was specifically asked to document reactions at the injection site, rashes, and any other systemic symptoms, including nausea, vomiting, diarrhea, tiredness, irritability, common cold, runny nose, sore throat, cough, earache, swollen glands, sore eyes, headache, stiff neck, muscle ache, joint pain, abdominal pain, loss of appetite, poor sleep, general discomfort, chills, and teething.

Clinical information was also obtained by frequent phone calls to the parent during which inquiries were made about each varicella-susceptible child in the family. For the first eight weeks after vaccination, the parent was contacted by a study nurse once a week and asked whether the child had experienced chickenpox or any sort of rash, an oral temperature of 38.9°C (102°F) or higher, convulsions or seizures, problems with coordination, or any other problems. After the first eight weeks, the parent was telephoned monthly and questioned about chickenpox or any rashes among children in the family.

The parent was instructed to telephone the study physician immediately if a varicella-like rash or any unusual reaction developed. A telephone sticker with this request and the physician's name and phone number was provided. Children suspected of having varicella or a varicella-like rash were examined by a physician or nurse. The onset of rash, the number of macules, papules, and vesicles, and any other signs and symptoms were documented, and an attempt was made to obtain vesicular fluid, a smear, and an acute-phase blood

specimen. A convalescent-phase serum sample was requested two to four weeks after the onset of disease.

Blood samples were obtained from each child immediately before injection and approximately eight weeks later. These samples were obtained to confirm the initial serologic status and to measure anti-body response in the vaccinated children and possible contagious spread in the controls.

Varicella Case Definition

Cases were classified on the basis of clinical or laboratory confirmation. Clinically confirmed cases were defined as those in which a study physician or nurse examined the child and diagnosed the condition as varicella. Two criteria had to be met for laboratory confirmation: (1) a clinical diagnosis of varicella made by either a study physician or nurse, and (2) varicella virus isolated in tissue cultures of lesions, seroconversion, or a fourfold or higher rise in titer between the acute- and convalescent-phase serum samples.

Laboratory Methods

Scrum samples were tested by the immune-adherence-hemagglutination assay, using commercial varicella antigens to measure human scrum antibody.²¹ The fluorescence assay of antibody to membrane antigen was used in place of the immune-adherence-hemagglutination assay in the rare instances in which the results of the latter were equivocal because of nonspecific agglutination or a prozone.²² For both assays, a titer of 1:2 or higher was considered positive.

Vesicle fluid obtained from clinical cases of chickenpox was transferred to human diploid fibroblast (MRC-5) cells and observed for two weeks for cytopathogenicity typical of varicella zoster. Isolates were identified after two to four serial passages in cell culture either by plaque-reduction neutralization or indirect immunofluorescence, using known positive and negative human serum samples specific for varicella.^{23,24} All samples were tested under code, and the laboratory personnel were blinded throughout the trial.

Statistical Methods

The minimal sample size was calculated using a one-tailed test²⁵ with a significance level (α) of 0.05 and a power (1- β) of 0.80. On the basis of a 2 per cent attack rate and a vaccine efficacy of 90 per cent, a minimum of approximately 415 children per group (or 830 seronegative children) was required to demonstrate efficacy. Additional children were enrolled to allow for attrition and injection of those who were initially scropositive.

Significance was calculated using either the chi-square test with Yates' correction or Fisher's exact test. 25,26

RESULTS

Study Population

A total of 956 children were enrolled in the study between September 9, 1982, and February 8, 1983; 491 received vaccine, and 465 received placebo. The mean age of both groups was 4.7 years. Fifty-three per cent of vaccine recipients and 49 per cent of controls were male. Approximately 95 per cent of both groups (468 vaccine and 446 placebo recipients) were initially seronegative. Forty-two children (23 vaccine and 19 placebo recipients) were found to be antibody-positive at the time of enrollment, though they had a negative history of varicella.

Table I shows the distribution, by family size, of the 914 initially scronegative children in the two study groups. The distribution was virtually identical, except that the group of families with three children had a slight excess of vaccine recipients. Ninety-four per

Each Family.

| NO. OF ENROLLED CHILDREN IN FAMILY | No. of Vaccine Recipients | No. of Placebo Recipients | Total |
|---|---------------------------------|---------------------------------|-------|
| 1 | 23 | 28 | 51 |
| 2 | 267 | 263 | 530 |
| 3 | 132 | 108 | 240 |
| 4 | 43 | 45 | 88 |
| 5 | 3 | 2 | 5 |
| Total | 468 | 446 | 914 |

cent of participants belonged to families with two or more children at risk of varicella.

Compliance during clinical and serologic follow-up was excellent, with no significant difference between vaccinated children and controls; 99 per cent of the children were followed clinically for 56 days after injection, and in 98 per cent blood samples were obtained before and after injection.

Clinical Reactions

Reports of temperatures and clinical symptoms throughout the 56-day observation period were summarized from the Vaccination Report Card of each participant and the physician's and nurse's records of telephone calls and examinations. No child was admitted to the hospital during this period.

Temperature Elevations

Oral temperatures of 38.9°C or higher were analyzed on a daily basis for the entire 56-day observation period. No significant difference was found between the temperatures reported in vaccinated and control subjects on any given day. During the first week after injection, less than 1 per cent of both groups had an oral temperature of 38.9°C or higher. During each of the subsequent seven weeks, no more than 2 per cent of either placebo or vaccine recipients had a reported temperature in this range. Initially seropositive vaccine and placebo recipients had the same low incidence of reported fever.

Injection-Site Reactions

During the first 48 hours after injection, 27 per cent of vaccinated children and 19 per cent of controls reported pain, redness, swelling, or rash at the injection site. On Days 2 to 3, the frequency of local reactions decreased markedly, to 7 and 3 per cent, respectively. Only pain and redness at the injection site were significantly more common (P<0.05) among vaccine recipients than among placebo recipients (pain, 26.4 vs. 17.5 per cent, and redness, 5 vs. 2.5 per cent, respectively). Few local reactions were reported after Day 3. Among initially scropositive vaccine and placebo re-

cipients, pain and redness occurred at about the same time and frequency.

Rashes

Twenty-eight "chickenpox-like" rashes (5 at the injection site and 23 elsewhere) were reported by parents of initially seronegative study participants during the eight-week observation period. Excluded were three rashes seen and diagnosed as varicella in placebo recipients. The overall incidence of rash among initially seronegative vaccine recipients was 4 per cent (19 of 468); the rate among seronegative placebo recipients was 2 per cent (9 of 446, P<0.054). Seroconversion occurred in all 19 vaccine recipients with rash; all 9 placebo recipients remained seronegative.

As shown in Figure 1, the reported onset of rash among vaccine and placebo recipients occurred between Days 0 to 30 and 0 to 43, respectively. The difference in temporal distributions between the two groups was not significant (P>0.1). The onset of rashes among vaccine recipients did not exhibit significant evidence of temporal clustering (P>0.08) when analyzed with the scan statistic of Naus.²⁷

A breakdown of rashes by group and site is shown in Table 2. Ten rashes (one at the injection site and nine at another site) were seen by a physician. The other 18 were not seen because the parent failed to contact a physician at the time of the rash.

Four of the five injection-site rashes occurred in vaccine recipients with a papule or induration developing at the injection site between Days 0 and 9 after vaccination. One of these rashes, which occurred on Days 7 and 8, was diagnosed by a physician as varicella-like. The fifth injection-site rash occurred in a placebo recipient who had a single papule on Day 17. The lesions persisted for an average of five days in vaccine recipients and four days in the one placebo recipient.

Of the 23 rashes at other sites, 9 were seen by a physician. Five of the nine (three in vaccine recipients and two in placebo recipients) were described as not varicella-like on the basis of appearance and distribution. Four of the nine rashes examined by a study physician were judged to be varicella-like; all four occurred in initially seronegative vaccine recipients in whom seroconversion occurred. Two were generalized papular rashes. In one child (Case 7) the rash began on Day 29, persisted for six days, and consisted of 18 papules. In the second child (Case 887) the rash began on Day 16, lasted for 15 days, and involved 14 papules, with four small crusted lesions. In the other two children (Cases 283 and 78) the rashes were limited to the face, began on Days 10 and 15, lasted one and six days, and produced one and five lesions, respectively. None of these four rashes were associated with a temperature elevation. No vesicles were observed or reported.

One seropositive vaccine recipient (Case 950) was reported to have a non-injection-site rash on Days 2

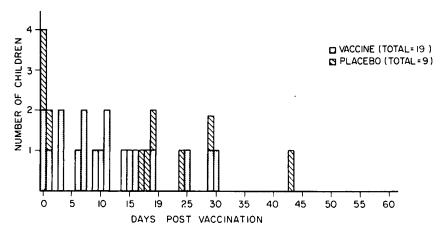


Figure 1. Onset of Varicella-like Rashes Reported among Initially Seronegative Vaccine and Placebo Recipients during the Eight-Week Follow-up Period.

and 3 after vaccination. The rash was not seen by a physician. The child had no change in antibody titer after vaccination.

Nonspecific Symptoms

The frequencies of other symptoms reported during the eight-week follow-up were approximately equal for all seronegative and seropositive vaccine and placebo recipients. The frequencies of these symptoms among initially seronegative vaccine and placebo recipients, respectively, were as follows: common cold, 63 and 65 per cent; cough, 45 and 48 per cent; irritability, 24 and 20 per cent; tiredness, 20 and 22 per cent; headache, 15 and 16 per cent; diarrhea, 12 and 14 per cent; poor sleep, 12 and 13 per cent; loss of appetite, 11 and 13 per cent; and earache, 11 and 13 per cent.

A recent article has suggested that Stage I Reye's syndrome may occur more frequently after chickenpox and upper respiratory infections than has previously been realized.²⁸ Therefore, we examined the frequency of vomiting with or without concurrent symptoms in susceptible vaccine and placebo recipients. Differences between the two groups were not significant. The specific rates for vaccine recipients and controls, respectively, were as follows: vomiting, 14 and 14 per cent; vomiting without concurrent diarrhea, 10 and 12 per cent; and vomiting and irritability without concurrent diarrhea, l and l per cent.

Serologic Response

Table 3 summarizes the varicella-antibody response rates among initially seronegative children who received vaccine. Antibody developed in 432 of the 461 vaccine recipients in whom blood specimens were obtained after vaccination, giving a seroconversion rate of 94 per cent and a geometric mean titer of 12.1 (range, 2 to 128). Children at all ages from 1 to 14 years responded similarly in terms of the seroconversion rate and antibody titer.

Among initially seronegative placebo recipients, seroconversion occurred in 1 per cent (6 of 439); the titers ranged from 4 to 32. No varicella-like rash and some of Mercel hebservation period (onset, Days 30, 42, and 50).

reported in these children or their vaccinated siblings. In two of the six families the sibling who received vaccine had no seroconversion, and in one family the vaccine recipient was initially seropositive and had no increase in antibody level after vaccination. It is probable that in these three families vaccine was inadvertently administered to the intended control child and placebo was given to the intended vaccine recipient. In the other three families, seroconversion occurred in both the vaccine and placebo recipients, and it is possible that subclinical spread of vaccine virus or natural virus occurred.

Among the 42 initially scropositive vaccine and placebo recipients, blood specimens were obtained before and after injection in all but one member of each group. The prevaccination geometric mean titer in the 22 initially seropositive children who received vaccine was 17.6 (range, 4 to 128); eight weeks after vaccination, it was 53.0 (range, 16 to 256). Ten of the 22 children (45 per cent) had a fourfold or higher rise in titer after vaccination. The 18 children who were initially seropositive and received placebo had little change in antibody titer. Their geometric mean titer before injection was 9.7 (range, 4 to 32); eight weeks later, it was 10.5 (range, 4 to 32).

Varicella Cases

During the course of the trial, 39 children were clinically diagnosed as having varicella. The distribution of cases by month of occurrence after injection is shown in Figure 2. The first case was diagnosed on December 16, 1982; the last case was reported on June 8, 1983, a week before the prearranged date for terminating the study. The incidence of disease was low from December through February, with the peak incidence of 12 cases occurring in May.

Table 2. Varicella-like Rashes Reported among Initially Seronegative Study Participants during the Eight Weeks after Vaccination.*

| | VACCINE RECIPIENTS | PLACEBO RECIPIENTS |
|------------------------------------|-----------------------|-----------------------|
| Injection-site rashes | 4 | 1 |
| Seen by physician (varicella-like) | (1) | (0) |
| Not seen by physician | (3) | (1) |
| Non-injection-site rashes | 15 | 8 |
| Seen by physician | | |
| Varicella-like | (4) | (0) |
| Not varicella-like | (3) | (2) |
| Not seen by physician | (8) | (6) |
| Total | 19 | 9 |

^{*}Excludes the three cases of varicella that occurred in placebo recipients during the eight-

For each of the 39 clinically diagnosed cases, the interval between receipt of vaccine or placebo and onset of varicella is shown in Figure 3. The mean interval between injection and onset of disease was 156 days (range, 4 to 38 weeks). The case diagnosed at four weeks occurred in a placebo recipient who was exposed to varicella in school and whose sibling was an initially seropositive vaccine recipient.

Of the 39 clinically diagnosed cases, 38 were confirmed by laboratory tests. The one case without laboratory confirmation occurred in a placebo recipient who refused to allow any specimens to be obtained. Of the 38 children with laboratory-confirmed cases, 19 had both positive viral isolate and seroconversion, 14 had seroconversion or a fourfold or higher rise in titer, and 5 had a positive viral isolate. The geometric mean titer in the 33 serologically confirmed cases was 191 (range, 64 to 512).

Protective Efficacy

Evaluation of the protective efficacy of the vaccine was based on comparison of the attack rate for laboratory-confirmed cases of natural varicella in the vaccine and placebo groups during the nine-month surveil-

Table 3. Seroconversion Rates and Geometric Mean Titers among Initially Seronegative Vaccine Recipients, According to Age.

| AGE | No. of Children | SEROCONVERSE | ON RATE | GEOMETRIC MEAN TITES |
|----------|--------------------|-----------------|----------|-------------------------|
| | VACCINATED | no, of children | per cent | WIEAN TITES |
| 12-14 mo | 16 | 15/15 | 100 | 13.9 |
| 15-17 mo | 16 | 14/15 | 93 | 11.6 |
| 18-23 mo | 26 | 24/25 | 96 | 11.5 |
| 2-4 yr | 199 | 189/195 | 97 | 13.4 |
| 5-14 yr | 211 | 190/211 | 90 | 10.4 |
| Total | 468 | 432/461 | 94 | 12.1 |

lance period (Table 4). Thirty-eight laboratory-confirmed cases of varicella were included in this analysis. The attack rate among vaccine recipients was 0 per cent (0 of 468); the rate among placebo recipients was 8.5 per cent (38 of 446). All 38 cases occurred in initially seronegative placebo recipients, giving the vaccine a protective efficacy of 100 per cent ($P < 10^{-9}$).

A more critical evaluation of the protective efficacy of the vaccine was made by analyzing the attack rates in 27 families in which a laboratory-confirmed case of natural varicella occurred and placed one or more initially seronegative vaccine recipients at risk (Table 4). Thirty-six of the children in these families received placebo and 33 received vaccine. All 27 primary cases occurred in placebo recipients, exposing 9 controls and 33 vaccine recipients. Varicella developed in 4 of the 9 placebo recipients (44 per cent) and in none of the 33 vaccine recipients exposed to a sibling with varicella. (An additional placebo recipient in one of the families contracted varicella one week after the

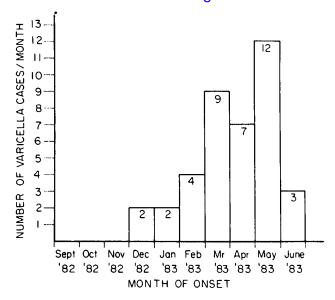


Figure 2. Distribution of Varicella Cases by Month of Onset.

termination of the study, increasing the secondary attack rate to 56 per cent (five of nine).) One vaccine recipient who had no antibody eight weeks after vaccination remained free of varicella when placed at risk. An analysis of the data based only on household exposures also showed that the protective efficacy of the vaccine was 100 per cent (P < 0.001).

Discussion

This study demonstrates the efficacy of the Oka/ Merck live attenuated varicella virus vaccine administered to healthy children before exposure. During the course of one varicella season, 38 laboratory-confirmed cases of varicella occurred in placebo recipients, whereas none occurred in recipients of vaccine.

The minimal clinical reactivity reported in this trial confirms our previous experience with the vaccine. 13 Among 914 initially seronegative children, only pain and redness at the injection site were reported more frequently among vaccine recipients than placebo recipients (P<0.05). Only 4 per cent (19 of 468) of the

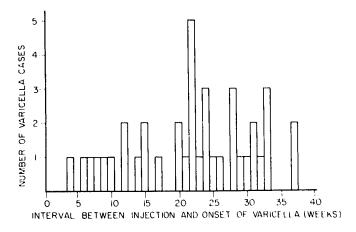


Figure 3. Interval between Injection and Onset of the 39 Clinically Diagnosed Cases of Varicella.

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Table 4. Attack Rate and Protective Efficacy on the Basis of Laboratory-Confirmed Cases among Initially Seronegative Vaccine and Placebo Recipients during the Nine-Month Surveillance Period.

| GROUP | | ALL PARTICIPANTS | | 27 Ho | USEHOLDS WITH 1 | 1 VACCINE RECIPIE | ENT EXPOSED TO 🥃 | SIBLING WITH VA | RICELLA |
|---------|--------------------|-----------------------|------------------|--------------------|----------------------------------|---|------------------------------------|-----------------------------|------------------------|
| | NO. OF CHILDREN | CASES OF VARICELLA | ATTACK RATE | NO. OF CHILDREN | PRIMARY CASES OF VARICELLA | NO. OF CHILDREN EXPOSED TO VARICELLA | SECONDARY CASES OF VARICELLA | SECONDARY ATTACK RATE | PROTECTIVI EFFICACY |
| Placebo | 446 | 38 | 8.5% (38/446) | 36 | 27 | 9 | 4 * | 44% (4/9) | 100% |
| Vaccine | 468 | 0 | 0% (0/468) | 33 | 0 | 33 | 0 | 0% (0/33) | |

^{*}A fifth case occurred one week after the study was terminated, increasing the secondary attack rate to 56 per cent (5 of 9 cases).

initially seronegative vaccine recipients had a reported varicella-like rash. All rashes were mild, nonvesicular, and well tolerated. The relatively high incidence of transient pain at the injection site reported in both vaccine and placebo recipients is largely attributable to the volume of the vaccine or placebo (1.0 ml) administered. The incidence of pain among vaccine recipients was in excess of that reported in previous studies using a 0.5-ml dose (unpublished data).

The vaccine was shown to be highly immunogenic in healthy children between the ages of 1 and 14 years. Over 94 per cent of the vaccine recipients had detectable varicella antibody eight weeks after vaccination. Careful monitoring of antibody levels in this population will be necessary to evaluate the duration of protection afforded by vaccination. Asano et al. have reported that 26 initially seronegative healthy children retained varicella antibody up to five years after vaccination with the Oka strain.²⁹ Seventeen of the children had one or more exposures to varicella during this period, and none contracted the disease. These results suggest long-term persistence of antibody and protective efficacy.

Lack of contagion of the vaccine virus was evaluated in our study. No clinical evidence of vaccine viral spread was reported. Laboratory evidence of varicella seroconversion in six placebo recipients does not agree with our previous study (unreported data) and other published reports. 18,30 Human error was probably the cause of varicella seroconversion in at least three of the six placebo recipients. However, in all six instances, a low incidence of subclinical spread of vaccine virus from vaccinated siblings or natural virus occurring in the community cannot be excluded.

The occurrence of herpes zoster after administration of live varicella vaccine has not yet been determined. Surveillance is being continued. To date, no case of zoster has been reported among any of the healthy children in this study. Takahashi has reported only one case of mild zoster among 4505 healthy children who received Oka strain varicella vaccine (personal communication).

The life-threatening complications of varicella in healthy persons include viral dissemination (encephalitis, pneumonitis, and so forth), bacterial infections,

five-year period 84 per cent of children hospitalized for varicella at a major U.S. children's hospital were immunologically normal.³ Varicella can be especially severe in adults, neonates infected in utero, immunocompromised patients, and those with preexisting conditions, 2,3,31,32

The results of this clinical trial provide preliminary evidence that administration of the live attenuated Oka/Merck varicella virus vaccine in healthy children is safe, highly immunogenic, and protective against natural varicella, a potentially serious illness. Further studies are warranted to determine the long-term safety of the vaccine, the incidence of zoster in recipients, and the duration of immunity provided by the vaccine in comparison to immunity from natural disease. If these studies reveal that the vaccine is safe and confers long-lasting protection, its use either alone or in combination with other pediatric vaccines in healthy children could reduce the morbidity and mortality associated with varicella.

We are indebted to the children and parents for their participation in this trial and to the physicians, nurses, administrators, and study personnel for their cooperation, especially to Horst Agerty, M.D., Alfred J. Carlson, Jr., M.D., Louis J. Casale, M.D., Joseph J. Cirotti, M.D., Theodore Clair, M.D., Charles H. Classen, M.D., Coulson A. Conn, M.D., Richard T. Ellison, M.D., J. Ronald Halenda, M.D., Richard Hartmann, M.D., Jeremy Lictman, M.D., Arthur N. Leibowitz, M.D., Vincent Menna, M.D., Dominic Menta, M.D., Alexander Randall, M.D., Richard Rissmiller, D.O., Ted Robinson, M.D., John Rodzvilla, M.D., William J. Sohn, M.D., George A. Starkweather, M.D., Stephen Townend, M.D., George R. Wade, M.D., Joseph H. Werner, M.D., Patricia Burns, R.N., Anne Hook, R.N., Patricia Manzi, R.N., and Linda Morrison for medical assistance; to Msgr. John J. Haydt, Rev. Donald Reilly, and Jane Hasset, B.A., for use of school facilities; to Mary McCaughtry, M.S., and David Morton, B.A., for laboratory assistance; to John Pleier, B.S., Gayland Ridley, M.S., Tim Schofield, M.A., and Sue Schwartz, B.A., for statistical and programming assistance; and to Christine Kirkpatrick, B.A., and Carol Shaw for assistance in data entry, administration, and manuscript preparation.

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INHIBITION OF ADRENAL STEROIDOGENESIS BY THE ANESTHETIC ETOMIDATE

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Abstract The use of the intravenous anesthetic etomidate for prolonged sedation has been associated with low levels of plasma cortisol and increased mortality. We measured the cortisol and aldosterone responses to ACTH stimulation in five patients receiving etomidate, and we also studied the direct effects of etomidate on enzymes in the rat steroidogenic pathway. One patient who was receiving a 20-hour infusion of etomidate (1.3 to 1.5 mg per kilogram of body weight per hour) had marked adrenocortical suppression that was still evident four days after etomidate was discontinued. Four surgical patients receiving etomidate during their operations were all found to have adrenal suppression four hours after the operation; mean (±S.D.) increases in cortisol and aldosterone after ACTH stimulation were only 1.8 \pm 0.5 μ g per deciliter and 0.5±1.1 ng per deciliter, respectively. In rat adrenal cells, etomidate produced a concentration-dependent blockade of the two mitochondrial cytochrome P-450-dependent enzymes, cholesterol-sidechain cleavage enzyme, and 11β -hydroxylase, without evident inhibition of the microsomal enzymes in the glucocorticoid pathway. Physicians should be aware that etomidate inhibits adrenal steroidogenesis, and they should consider treating selected patients with corticosteroids if etomidate is used. (N Engl J Med 1984; 310:1415-21.)

ETOMIDATE is an intravenous sedative-hypnotic that has been used for the induction and maintenance of anesthesia and for prolonged sedation of critically ill patients. The drug is administered by either

bolus injection or continuous infusion¹ and is characterized by a rapid onset of action and recovery,2 excellent cardiovascular stability,3 and the absence of histamine release.4 Although only recently available in the United States, etomidate has gained wide acceptance in Europe as an anesthetic for patients with cardiovascular instability⁵ and as a sedative for ventilator-dependent patients.6

Recently, an intensive-care unit in England report-

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Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of a National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of the National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of the National Research Services England Journal of Medicine Award (AM 06962) from the National Institutes of Health. Dr. Kan is the recipient of the National Research Services England Journal of Medicine Award (AM 06962) from the National Research Services England Journal of Medicine Award (AM 06962) from the National Research Services England Journal of Medicine Award (AM 06962) from the National Research Services England Journa From the NEJM Archive. Copyright © 2012

Exhibit 250

EXHIBIT 251

Case 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 373 of 497 Use caution when administering ProQuad to children with

These highlights do not include all the information needed to use ProQuad safely and effectively. See full prescribing information for ProQuad.

ProQuad®

Measles, Mumps, Rubella and Varicella Virus Vaccine Live Suspension for subcutaneous injection Initial U.S. Approval: 2005

-----INDICATIONS AND USAGE -----

ProQuad is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age. (1)

-----DOSAGE AND ADMINISTRATION --

A 0.5-mL dose for subcutaneous injection only. (2.1)

- The first dose is usually administered at 12 to 15 months of age.
- A second dose, if needed, is usually administered at 4 to 6 years of age. (2.1)

---- DOSAGE FORMS AND STRENGTHS ------

Suspension for injection (0.5-mL dose) supplied as a lyophilized vaccine to be reconstituted using only accompanying sterile diluent.

-----CONTRAINDICATIONS -----

- History of anaphylactic reaction to neomycin or hypersensitivity to gelatin or any other component of the vaccine. (4.1)
- Primary or acquired immunodeficiency states. (4.2)
- Family history of congenital or hereditary immunodeficiency. (4.2)
- Immunosuppressive therapy. (4.2, 7.3)
- Active untreated tuberculosis or febrile illness (>101.3°F or >38.5°C). (4.3)
- Pregnancy. (4.4, 8.1, 17)

----- WARNINGS AND PRECAUTIONS-----

- Administration of ProQuad (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with M-M-R® II and VARIVAX® administered separately. (5.1, 6.1, 6.3)
- Use caution when administering ProQuad to children with a history of cerebral injury or seizures or any other condition in which stress due to fever should be avoided. (5.2)
- Use caution when administering ProQuad to children with anaphylaxis or immediate hypersensitivity to eggs (5.3) or contact hypersensitivity to neomycin. (5.4)

- thrombocytopenia. (5.5)
- Avoid close contact with high-risk individuals susceptible to varicella since transmission of varicella vaccine virus may occur between vaccinees and susceptible contacts. (5.8)
- Defer vaccination for at least 3 months following blood or plasma transfusions, or administration of immune globulins (IG). (5.9, 7.1)
- Avoid using salicylates for 6 weeks after vaccination with ProQuad. (5.10, 7.2, 17)
- Avoid pregnancy for 3 months following vaccination with measles, mumps, rubella, and/or varicella vaccines. (8.1, 17)

----- ADVERSE REACTIONS ------

- The most frequent vaccine-related adverse events reported in ≥5% of subjects vaccinated with ProQuad were:
 - injection-site reactions (pain/tenderness/soreness, erythema, and swelling)
 - fever
 - irritability. (6.1)
- Systemic vaccine-related adverse events that were reported at a significantly greater rate in recipients of ProQuad than in recipients of the component vaccines administered concomitantly were:
 - fever
 - measles-like rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---- DRUG INTERACTIONS ----

- Tuberculin testing should be administered anytime before, simultaneously with, or at least 4 to 6 weeks after ProQuad. (7.4)
- ProQuad may be administered concomitantly with Haemophilus influenzae type b conjugate vaccine and/or hepatitis B vaccine at separate injection sites. (7.5)
- ProQuad may be administered concomitantly with pneumococcal 7-valent conjugate vaccine and/or hepatitis A vaccine (inactivated) at separate injection sites. (7.5)

--- USE IN SPECIFIC POPULATIONS ----

Pregnancy: Do not administer ProQuad to females who are pregnant. Pregnancy should be avoided for 3 months following vaccination with ProQuad. (4.4, 8.1, 17)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2018

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Exhibit 251

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ProQuad® is a vaccine indicated for active immunization for the prevention of measles, mumps, rubella, and varicella in children 12 months through 12 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose and Schedule

FOR SUBCUTANEOUS ADMINISTRATION ONLY

Each 0.5-mL dose of ProQuad is administered subcutaneously.

The first dose is usually administered at 12 to 15 months of age but may be given anytime through 12 years of age.

If a second dose of measles, mumps, rubella, and varicella vaccine is needed, ProQuad may be used. This dose is usually administered at 4 to 6 years of age. At least 1 month should elapse between a dose of a measles-containing vaccine such as M-M-R® II (measles, mumps, and rubella virus vaccine live) and a dose of ProQuad. At least 3 months should elapse between a dose of varicella-containing vaccine and ProQuad.

2.2 Preparation for Administration

CAUTION: Preservatives, antiseptics, detergents, and other anti-viral substances may inactivate the vaccine. Use only sterile syringes that are free of preservatives, antiseptics, detergents, and other anti-viral substances for reconstitution and injection of ProQuad.

Withdraw the entire volume of the supplied diluent into a syringe. Use only the diluent supplied with the vaccine since it is free of preservatives or other anti-viral substances.

Inject the entire content of the syringe into the vial containing the powder. Gently agitate to dissolve completely.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Visually inspect the vaccine before and after reconstitution prior to administration. Before reconstitution, the lyophilized vaccine is a white to pale yellow compact crystalline plug. ProQuad, when reconstituted, is a clear pale yellow to light pink liquid.

Withdraw the entire amount of the reconstituted vaccine from the vial into the same syringe and inject the entire volume.

TO MINIMIZE LOSS OF POTENCY, THE VACCINE SHOULD BE ADMINISTERED IMMEDIATELY AFTER RECONSTITUTION. IF NOT USED IMMEDIATELY, THE RECONSTITUTED VACCINE MAY BE STORED AT ROOM TEMPERATURE, PROTECTED FROM LIGHT, FOR UP TO 30 MINUTES. DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

2.3 Method of Administration

Inject the vaccine subcutaneously into the outer aspect of the deltoid region of the upper arm or into the higher anterolateral area of the thigh.

Use With Other Vaccines

Use different injection sites to administer each vaccine if other vaccines are administered concomitantly. [See Drug Interactions (7.5).]

3 DOSAGE FORMS AND STRENGTHS

ProQuad is a suspension for injection supplied as a 0.5-mL single dose vial of lyophilized vaccine to be reconstituted using the sterile diluent supplied [see How Supplied/Storage and Handling (16)].

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer ProQuad to individuals with a history of anaphylactic reactions to neomycin. If vaccination with ProQuad is medically necessary for such individuals, they are advised to consult an allergist or immunologist and should receive ProQuad only in settings where anaphylactic reactions can be appropriately managed.

Do not administer ProQuad to individuals with a history of hypersensitivity to gelatin or any other component of the vaccine or following previous vaccination with ProQuad, VARIVAX® (varicella virus

vaccine live), or any measles-, mumps-, or rubella-containing vaccine [see Description (11) and Warnings and Precautions (5) for exceptions].

4.2 Immunosuppression

Do not administer ProQuad to individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic system; or to individuals on immunosuppressive therapy (including high-dose systemic corticosteroids) [see Drug Interactions (7.3)]. Vaccination with a live, attenuated vaccine, such as varicella, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive drugs. ProQuad may be used by individuals who are receiving topical corticosteroids or low-dose corticosteroids, as are commonly used for asthma prophylaxis or in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Do not administer ProQuad to individuals with primary and acquired immunodeficiency states, including AIDS or other clinical manifestations of infection with human immunodeficiency viruses; cellular immune deficiencies; and hypogammaglobulinemic and dysgammaglobulinemic states. Measles inclusion body encephalitis, pneumonitis, and death as a direct consequence of disseminated measles vaccine virus infection have been reported in severely immunocompromised individuals inadvertently vaccinated with measles-containing vaccine. In addition, disseminated varicella vaccine virus infection has been reported in children with underlying immunodeficiency disorders who were inadvertently vaccinated with a varicella-containing vaccine {1}.

Do not administer ProQuad to individuals with a family history of congenital or hereditary immunodeficiency, unless the immune competence of the potential vaccine recipient is demonstrated.

4.3 Concurrent Illness

Do not administer ProQuad to individuals with active untreated tuberculosis or to individuals with an active febrile illness with fever >101.3°F (>38.5°C).

4.4 Pregnancy

Do not administer ProQuad to individuals who are pregnant because the effects of the vaccine on fetal development are unknown. If vaccination of postpubertal females is undertaken, pregnancy should be avoided for three months following administration of ProQuad [see Use in Specific Populations (8.1) and Patient Counseling Information (17)].

5 WARNINGS AND PRECAUTIONS

5.1 Fever and Febrile Seizures

Administration of ProQuad (dose 1) to children 12 to 23 months old who have not been previously vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections, is associated with higher rates of fever and febrile seizures at 5 to 12 days after vaccination when compared to children vaccinated with dose 1 of both M-M-R II and VARIVAX administered separately [see Adverse Reactions (6.3)].

5.2 History of Cerebral Injury or Seizures

Exercise caution when administering ProQuad to persons with a history of cerebral injury, individual or family history of convulsions, or any other condition in which stress due to fever should be avoided. Healthcare providers should be alert to the temperature elevations that may occur following vaccination.

5.3 Hypersensitivity to Eggs

Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Persons with a history of anaphylactic or other immediate hypersensitivity reactions (e.g., hives, swelling of the mouth and throat, difficulty breathing, hypotension, or shock) subsequent to egg ingestion may be at an enhanced risk of immediate-type hypersensitivity reactions after receiving vaccines containing traces of chick embryo antigen. Carefully evaluate the potential risk-to-benefit ratio before considering vaccination in such cases. Such individuals may be vaccinated with extreme caution; adequate treatment should be readily available should a reaction occur [see Contraindications (4.1)] {2}.

Children with egg allergy are at low risk for anaphylactic reactions to measles-containing vaccines (including M-M-R II), and skin testing of children allergic to eggs is not predictive of reactions to M-M-R II vaccine. Persons with allergies to chickens or feathers are not at increased risk of reaction to the vaccine {2}.

5.4 Contact Hypersensitivity to Neomycin

Most often, neomycin allergy manifests as a contact dermatitis, which is not a contraindication to receiving measles-, mumps-, rubella-, or varicella-containing vaccine.

5.5 Thrombocytopenia

Carefully evaluate the potential risk-to-benefit ratio before considering vaccination with ProQuad in children with thrombocytopenia or in those who experienced thrombocytopenia after vaccination with a previous dose of measles, mumps, rubella, and/or varicella vaccine. No clinical data are available regarding the development or worsening of thrombocytopenia in individuals vaccinated with ProQuad. Cases of thrombocytopenia have been reported after primary vaccination with measles vaccine; measles, mumps, and rubella vaccine; after varicella vaccination; and following re-vaccination with measles vaccine or M-M-R II [see Adverse Reactions (6.2)].

5.6 Use for Post-Exposure Prophylaxis

The safety and efficacy of ProQuad for use after exposure to measles, mumps, rubella, or varicella have not been established.

5.7 Use in HIV-Infected Children

The safety and efficacy of ProQuad for use in children known to be infected with human immunodeficiency viruses have not been established.

5.8 Risk of Vaccine Virus Transmission

Post-licensing experience with VARIVAX suggests that transmission of varicella vaccine virus may occur between healthy vaccine recipients (who develop or do not develop a varicella-like rash) and contacts susceptible to varicella, as well as high-risk individuals susceptible to varicella.

High-risk individuals susceptible to varicella include:

- Immunocompromised individuals;
- Pregnant women without documented positive history of varicella (chickenpox) or laboratory evidence of prior infection;
- Newborn infants of mothers without documented positive history of varicella or laboratory evidence of prior infection and all newborn infants born at <28 weeks gestation regardless of maternal varicella immunity.

Vaccine recipients should attempt to avoid, to the extent possible, close association with high-risk individuals susceptible to varicella for up to 6 weeks following vaccination. In circumstances where contact with high-risk individuals susceptible to varicella is unavoidable, the potential risk of transmission of the varicella vaccine virus should be weighed against the risk of acquiring and transmitting wild-type varicella virus.

Excretion of small amounts of the live, attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7 to 28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk. However, transmission of the rubella vaccine virus to infants via breast milk has been documented [see Use in Specific Populations (8.2)].

There are no reports of transmission of the more attenuated Enders' Edmonston strain of measles virus or the Jervl Lvnn™ strain of mumps virus from vaccine recipients to susceptible contacts.

5.9 Immune Globulins and Transfusions

Immune globulins (IG) administered concomitantly with ProQuad contain antibodies that may interfere with vaccine virus replication and decrease the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG.

The appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (e.g., 5 months for Varicella Zoster Immune Globulin [VZIG]) {2}. Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination {2}. [See Drug Interactions (7.1).]

5.10 Salicylate Therapy

Avoid the use of salicylates (aspirin) or salicylate-containing products in children and adolescents 12 months through 12 years of age, for six weeks following vaccination with ProQuad due to the association of Reye syndrome with aspirin therapy and wild-type varicella infection. [See Drug Interactions (7.2) and Patient Counseling Information (17).]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. Vaccine-related adverse reactions reported during clinical trials were assessed by the study investigators to be possibly, probably, or definitely vaccine-related and are summarized below.

Children 12 Through 23 Months of Age Who Received a Single Dose of ProQuad

Frozen ProQuad or refrigerator-stable ProQuad was administered to 6038 children 12 through 23 months of age involved in clinical trials without concomitant administration with other vaccines. The safety of frozen ProQuad (N=4497) was compared with the safety of M-M-R II and VARIVAX given concomitantly (N=2038) at separate injection sites. The safety profile for ProQuad was similar to the component vaccines. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for 98% of children in each group. Few subjects (<0.1%) who received ProQuad discontinued the study due to an adverse reaction. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 67.2% White; 12.0% African-American; 10.6% Hispanic; 5.0% Asian/Pacific; 3.4% other; 1.0% multiracial; 0.2% American Indian; 0.2% European; 0.2% Indian; and 0.1% Polynesian. The racial distribution of the control group was similar to that of the group who received ProQuad. The gender distribution across the studies following a first dose of ProQuad was 51.8% male and 48.2% female. The gender distribution of the control group was similar to that of the group who received ProQuad. Vaccine-related injection-site and systemic adverse reactions observed among recipients of ProQuad or M-M-R II and VARIVAX at a rate of at least 1% are shown in Table 1. Systemic vaccine-related adverse reactions that were reported at a significantly greater rate in individuals who received a first dose of ProQuad than in individuals who received first doses of M-M-R II and VARIVAX concomitantly at separate injection sites were fever (≥102°F [≥38.9°C] oral equivalent or abnormal) (21.5% versus 14.9%, respectively, risk difference 6.6%, 95% CI: 4.6, 8.5), and measles-like rash (3.0% versus 2.1%, respectively, risk difference 1.0%, 95% CI: 0.1, 1.8). Both fever and measles-like rash usually occurred within 5 to 12 days following the vaccination, were of short duration, and resolved with no long-term sequelae. Pain/tenderness/soreness at the injection site was reported at a statistically lower rate in individuals who received ProQuad than in individuals who received M-M-R II and VARIVAX concomitantly at separate injection sites (22.0% versus 26.8%, respectively, risk difference -4.8%, 95% CI: -7.1, -2.5). The only vaccine-related injection-site adverse reaction that was more frequent among recipients of ProQuad than recipients of M-M-R II and VARIVAX was rash at the injection site (2.4% versus 1.6%. respectively, risk difference 0.9%, 95% CI: 0.1, 1.5).

Table 1: Vaccine-Related Injection-Site and Systemic Adverse Reactions
Reported in ≥1% of Children Who Received ProQuad Dose 1 or M-M-R II and VARIVAX
at 12 to 23 Months of Age (0 to 42 Days Postvaccination)

| Adverse Reactions | ProQuad (frozen) (N=4497) (n=4424) % | M-M-R II and VARIVAX (N=2038) (n=1997) % |
|---------------------------------------|--|---|
| Injection Site* | | |
| Pain/tenderness/soreness [†] | 22.0 | 26.7 |
| Erythema [†] | 14.4 | 15.8 |
| Swelling [†] | 8.4 | 9.8 |
| Ecchymosis | 1.5 | 2.3 |
| Rash | 2.3 | 1.5 |
| Systemic | | |
| Fever ^{†,‡} | 21.5 | 14.9 |
| Irritability | 6.7 | 6.7 |
| Measles-like rash [†] | 3.0 | 2.1 |
| Varicella-like rash [†] | 2.1 | 2.2 |
| Rash (not otherwise specified) | 1.6 | 1.4 |
| Upper respiratory infection | 1.3 | 1.1 |
| Viral exanthema | 1.2 | 1.1 |
| Diarrhea | 1.2 | 1.3 |

5

- * Injection-site adverse reactions for M-M-R II and VARIVAX are based on occurrence with either of the vaccines administered.
- † Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 0 to 4 postvaccination.
- [‡] Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.
- N = number of subjects vaccinated.
- n = number of subjects with safety follow-up.

Rubella-like rashes were observed in <1% of subjects following a first dose of ProQuad.

In these clinical trials, two cases of herpes zoster were reported among 2108 healthy subjects 12 through 23 months of age who were vaccinated with their first dose of ProQuad and followed for 1 year. Both cases were unremarkable and no sequelae were reported.

Clinical safety of the refrigerator-stable formulation of ProQuad (N=1006) was compared with that of the licensed frozen formulation of ProQuad (N=513) for 42 days postvaccination in children 12 through 23 months of age. The race distribution of the study subjects across these studies following a first dose of ProQuad was as follows: 73.0% White; 9.3% Hispanic; 8.7% African-American; 3.9% multiracial; 2.6% Asian/Pacific; 0.9% Indian; 0.8% European; 0.5% Polynesian; 0.1% American Indian; and 0.1% African. The gender distribution across the studies following a first dose of ProQuad was 49.9% male and 50.1% female.

Injection-site and systemic adverse reactions observed among recipients of ProQuad refrigerator-stable and ProQuad at a rate of at least 1% are shown in Table 2. The safety profiles were comparable for the two different formulations.

Table 2: Vaccine-Related Injection-Site and Systemic Adverse Reactions
Reported in ≥1% of Children Who Received ProQuad Refrigerator-Stable and ProQuad Frozen
at 12 to 23 Months of Age (0 to 42 Days Postvaccination)

| Adverse Reactions | ProQuad (refrigerator-stable) (N=1006) (n=983) % | ProQuad (frozen) (N=513) (n=500) % | |
|-----------------------------|--|--|--|
| Injection Site | | | |
| Pain/tenderness/soreness* | 29.6 | 30.4 | |
| Erythema* | 17.8 | 18.0 | |
| Swelling* | 8.7 | 9.2 | |
| Hemorrhage | 1.5 | 1.2 | |
| Systemic | | | |
| Fever*,† | 10.6 | 9.0 | |
| Irritability | 4.9 | 6.6 | |
| Measles-like rash* | 4.9 | 6.0 | |
| Varicella-like rash* | 3.0 | 1.8 | |
| Upper respiratory infection | 1.7 | 1.4 | |
| Vomiting | 1.4 | 1.4 | |
| Diarrhea | 1.3 | 8.0 | |
| Nasopharyngitis | 1.2 | 8.0 | |
| Eczema | 1.0 | 1.2 | |

^{*} Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.

Children 15 to 31 Months of Age Who Received a Second Dose of ProQuad

In 5 clinical trials, 2780 healthy children were vaccinated with ProQuad (dose 1) at 12 to 23 months of age and then administered a second dose approximately 3 to 9 months later. The race distribution of the study subjects across these studies following a second dose of ProQuad was as follows: 64.4% White; 14.1% African-American; 12.0% Hispanic; 5.9% other; 3.5% Asian/Pacific; and 0.1% American Indian. The gender distribution across the studies following a second dose of ProQuad was 51.5% male and 48.5% female. Children in these open-label studies were monitored for at least 28 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for approximately 97% of children overall. Vaccine-related injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 3. In these trials, the overall rates of systemic

[†] Temperature reported as oral equivalent (≥102°F) or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

adverse reactions after ProQuad (dose 2) were comparable to, or lower than, those seen with the first dose. In the subset of children who received both ProQuad dose 1 and dose 2 in these trials (N=2408) with follow-up for fever, fever ≥102.2°F (≥38.9°C) was observed significantly less frequently days 1 to 28 after the second dose (10.8%) than after the first dose (19.1%) (risk difference 8.3%, 95% CI: 6.4, 10.3). Fevers ≥102.2°F (≥38.9°C) days 5 to 12 after vaccinations were also reported significantly less frequently after dose 2 (3.9%) than after dose 1 (13.6%) (risk difference 9.7%, 95% CI: 8.1, 11.3). In the subset of children who received both doses and for whom injection-site reactions were reported (N=2679), injection-site erythema was noted significantly more frequently after ProQuad (dose 2) as compared to ProQuad (dose 1) (12.6% and 10.8%, respectively, risk difference -1.8, 95% CI: -3.3, -0.3); however, pain and tenderness at the injection site was significantly lower after dose 2 (16.1%) as compared with after dose 1 (21.9%) (risk difference, 5.8%, 95% CI: 4.1, 7.6). Two children had febrile seizures after ProQuad (dose 2); both febrile seizures were thought to be related to a concurrent viral illness [see Adverse Reactions (6.3) and Clinical Studies (14)]. These studies were not designed or statistically powered to detect a difference in rates of febrile seizure between recipients of ProQuad as compared to M-M-R II and VARIVAX. The risk of febrile seizure has not been evaluated in a clinical study comparing the incidence rate after ProQuad (dose 2) with the incidence rate after concomitant M-M-R II (dose 2) and VARIVAX (dose 2). [See Adverse Reactions (6.1), Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX.1

Table 3: Vaccine-Related Injection-Site and Systemic Adverse Reactions
Reported in ≥1% of Children Who Received ProQuad Dose 1 at 12 to 23 Months of Age and Dose 2
at 15 to 31 Months of Age (1 to 28 Days Postvaccination)

| Adverse Reactions | ProQuad Dose 1 (N=3112) (n=3019) % | ProQuad Dose 2 (N=2780) (n=2695) % |
|--------------------------------|--|--|
| Injection-Site | | |
| Pain/tenderness/soreness* | 21.4 | 15.9 |
| Erythema* | 10.7 | 12.4 |
| Swelling* | 8.0 | 8.5 |
| Injection-site bruising | 1.1 | 0.0 |
| Systemic | | |
| Fever*,† | 20.4 | 8.3 |
| Irritability | 6.0 | 2.4 |
| Measles-like/Rubella-like rash | 4.3 | 0.9 |
| Varicella-like/Vesicular rash | 1.5 | 0.1 |
| Diarrhea | 1.3 | 0.6 |
| Upper respiratory infection | 1.3 | 1.4 |
| Rash (not otherwise specified) | 1.2 | 0.6 |
| Rhinorrhea | 1.1 | 1.0 |

^{*} Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.

Children 4 to 6 Years of Age Who Received ProQuad After Primary Vaccination with M-M-R II and VARIVAX

In a double-blind clinical trial, 799 healthy 4- to 6-year-old children who received M-M-R II and VARIVAX at least 1 month prior to study entry were randomized to receive ProQuad and placebo (N=399), M-M-R II and placebo concomitantly (N=205) at separate injection sites, or M-M-R II and VARIVAX (N=195) concomitantly at separate injection sites [see Clinical Studies (14)]. Children in these studies were monitored for up to 42 days postvaccination using vaccination report card-aided surveillance. Safety follow-up was obtained for >98% of children in each group. The race distribution of the study subjects following a dose of ProQuad was as follows: 78.4% White; 12.3% African-American; 3.8% Hispanic; 3.5% other; and 2.0% Asian/Pacific. The gender distribution following a dose of ProQuad was 52.1% male and 47.9% female. Injection-site and systemic adverse reactions observed after Dose 1 and 2 of ProQuad at a rate of at least 1% are shown in Table 4. [See Clinical Studies (14).]

Table 4: Vaccine-Related Injection-Site and Systemic Adverse Reactions

[†] Temperature reported as elevated or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

Reported in ≥1% of Children Previously Vaccinated with M-M-R II and VARIVAX Who Received ProQuad + Placebo, M-M-R II + Placebo, or M-M-R II + VARIVAX at 4 to 6 Years of Age (1 to 43 Days Postvaccination)

| Adverse Reactions | ProQuad + Placebo (N=399) (n=397) % | | (N= | + Placebo =205) =205) % | VAR (N= (n= | R II + IVAX 195) 193) % |
|-----------------------------|--|---------|----------|----------------------------------|-------------------|-------------------------------------|
| Systemic | | | | | | |
| Fever*,† | 2. | 5 | 2.0 | 0 | 4. | 1 |
| Cough | 1. | 3 | 0. | 5 | 0. | 5 |
| Irritability | 1. | 0 | 0. | 5 | 1. | 0 |
| Headache | 0.8 | | 1.5 | | 1.6 | |
| Rhinorrhea | 0.5 | | 1.0 | | 0.5 | |
| Nasopharyngitis | 0. | 0.3 | | 1.0 | | 0 |
| Vomiting | 0. | | 1.0 | | 0.5 | |
| Upper respiratory infection | 0. | 0 | 0.0 | | 1.0 | |
| | ProQuad | Placebo | M-M-R II | Placebo | M-M-R II | VARIVAX |
| | % | % | % | % | % | % |
| Injection-Site | | | | | | |
| Pain* | 41.1 | 34.5 | 36.6 | 34.1 | 35.2 | 36.8 |
| Erythema* | 24.4 | 13.4 | 15.6 | 14.1 | 14.5 | 15.5 |
| Swelling* | 15.6 | 8.1 | 10.2 | 8.8 | 7.8 | 10.9 |
| Bruising | 3.5 | 3.8 | 2.4 | 3.4 | 1.6 | 2.1 |
| Rash | 1.5 | 1.3 | 0.0 | 0.0 | 0.5 | 0.0 |
| Pruritus | 1.0 | 0.3 | 0.0 | 0.0 | 0.0 | 1.0 |
| Nodule | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.0 |

^{*} Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.

Safety in Trials That Evaluated Concomitant Use with Other Vaccines

ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine

In an open-label clinical trial, 1434 children were randomized to receive ProQuad given with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly (N=949) or non-concomitantly with ProQuad given first and the other vaccines 6 weeks later (N=485). No clinically significant differences in adverse events were reported between treatment groups [see Clinical Studies (14)]. The race distribution of the study subjects who received ProQuad was as follows: 70.7% White; 10.9% Asian/Pacific; 10.7% African-American; 4.5% Hispanic; 3.0% other; and 0.2% American Indian. The gender distribution of the study subjects who received ProQuad was 53.6% male and 46.4% female.

<u>ProQuad Administered with Pneumococcal 7-valent Conjugate Vaccine and/or Hepatitis A Vaccine, Inactivated</u>

In an open-label clinical trial, 1027 healthy children 12 to 23 months of age were randomized to receive ProQuad (dose 1) and pneumococcal 7-valent conjugate vaccine (dose 4) concomitantly (N=510) or non-concomitantly at different clinic visits (N=517). The race distribution of the study subjects was as follows: 65.2% White; 15.1% African-American; 10.0% Hispanic; 6.6% other; and 3.0% Asian/Pacific. The gender distribution of the study subjects was 54.5% male and 45.5% female. Injection-site and systemic adverse reactions observed among recipients of ProQuad administered concomitantly or non-concomitantly with pneumococcal 7-valent conjugate vaccine at a rate of at least 1% are shown in Table 5. No clinically significant differences in adverse reactions were reported between the concomitant and non-concomitant treatment groups [see Clinical Studies (14)].

Table 5: Vaccine-Related Injection-Site and Systemic Adverse Reactions

Reported in ≥1% of Children Who Received ProQuad (dose 1) Concomitantly or Non-Concomitantly with PCV7* (dose 4) at the First Visit (1 to 28 Days Postvaccination)

[†] Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

| Adverse Reactions | ProQuad + PCV7 (N=510) (n=498) % | PCV7 (N=258) (n=250) % | ProQuad (N=259) (n=255) % | |
|-------------------------------|---|---------------------------------|------------------------------------|--|
| Injection-Site - ProQuad | | | | |
| Pain [†] | 24.9 | N/A | 24.7 | |
| Erythema [†] | 12.4 | N/A | 11.0 | |
| Swelling [†] | 10.8 | N/A | 7.5 | |
| Bruising | 2.0 | N/A | 1.6 | |
| Injection-Site - PCV7 | | | | |
| Pain [†] | 30.5 | 29.6 | N/A | |
| Erythema [†] | 21.1 | 24.4 | N/A | |
| Swelling [†] | 17.9 | 20.0 | N/A | |
| Bruising | 1.6 | 1.2 | N/A | |
| Systemic | | | | |
| Fever ^{†,‡} | 15.5 | 10.0 | 15.3 | |
| Measles-like rash | 4.4 | 8.0 | 5.1 | |
| Irritability | 3.8 | 3.6 | 3.5 | |
| Upper respiratory infection | 1.6 | 8.0 | 1.2 | |
| Varicella-like/vesicular rash | 1.6 | 0.0 | 1.2 | |
| Diarrhea | 0.8 | 1.2 | 1.2 | |
| Vomiting | 0.6 | 0.8 | 1.2 | |
| Rash | 0.4 | 0.0 | 1.2 | |
| Somnolence | 0.0 | 0.0 | 1.2 | |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine, dose 4.

N/A = Not applicable.

In an open-label clinical trial, 699 healthy children 12 to 23 months of age were randomized to receive 2 doses of VAQTA® (hepatitis A vaccine, inactivated) (N=352) or 2 doses of VAQTA concomitantly with 2 doses of ProQuad (N=347) at least 6 months apart. An additional 1101 subjects received 2 doses of VAQTA alone at least 6 months apart (non-randomized), resulting in 1453 subjects receiving 2 doses of VAQTA alone (1101 non-randomized and 352 randomized) and 347 subjects receiving 2 doses of VAQTA concomitantly with ProQuad (all randomized). The race distribution of the study subjects following a dose of ProQuad was as follows: 47.3% White; 42.7% Hispanic; 5.5% other; 2.9% African-American; and 1.7% Asian/Pacific. The gender distribution of the study subjects following a dose of ProQuad was 49.3% male and 50.7% female. Vaccine-related injection-site adverse reactions (days 1 to 5 postvaccination) and systemic adverse events (days 1 to 14 post VAQTA and days 1 to 28 post ProQuad vaccination) observed among recipients of VAQTA and ProQuad administered concomitantly with VAQTA at a rate of at least 1% are shown in Tables 6 and 7, respectively. In addition, among the randomized cohort, in the 14 days after each vaccination, the rates of fever (including all vaccine- and non-vaccine-related reports) were significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 1 (22.0%) as compared to subjects given dose 1 of VAQTA without ProQuad (10.8%). However, rates of fever were not significantly higher in subjects who received ProQuad with VAQTA concomitantly after dose 2 (12.5%) as compared to subjects given dose 2 of VAQTA without ProQuad (9.4%). In post-hoc analyses, these rates were significantly different for dose 1 (relative risk (RR) 2.03 [95% CI: 1.42, 2.94]), but not dose 2 (RR 1.32 [95% CI: 0.82, 2.13]). Rates of injection-site adverse reactions and other systemic adverse events were lower following a second dose than following the first dose of both vaccines given concomitantly.

Table 6: Vaccine-Related Injection-Site Adverse Reactions
Reported in ≥1% of Children Who Received VAQTA or ProQuad Concomitantly with VAQTA
1 to 5 Days After Vaccination with VAQTA or VAQTA and ProQuad

| 1 to 5 bays Aiter vaccination with vacta of vacta and 1 located | | | | | | | |
|---|-------------------------------|-------------------------------|-------------------------------|---------------------------------------|--|--|--|
| | D | ose 1 | | Dose 2 | | | |
| Adverse Reactions | VAQTA (N=1453) (n=1412) | ProQuad + VAQTA (N=347) | VAQTA (N=1301) (n=1254) | ProQuad + VAQTA (N=292) (n=264) | | | |
| | % | (n=328) | (II-1254) % | (H=20 4) % | | | |

[†] Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination.

[‡] Temperature reported as elevated (≥102°F, oral equivalent) or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

| | | % | | |
|--------------------------|------|------|------|------|
| | | | | |
| Injection-Site - VAQTA | | | | |
| Pain/tenderness* | 29.2 | 27.1 | 30.1 | 25.0 |
| Erythema* | 13.5 | 12.5 | 14.3 | 11.7 |
| Swelling* | 7.1 | 9.1 | 9.0 | 8.0 |
| Injection-site bruising | 1.9 | 2.4 | 1.0 | 0.8 |
| Injection-Site - ProQuad | | | | |
| Pain/tenderness* | N/A | 30.5 | N/A | 26.2 |
| Erythema* | N/A | 13.4 | N/A | 12.9 |
| Swelling* | N/A | 6.7 | N/A | 6.5 |
| Injection-site bruising | N/A | 1.5 | N/A | 0.4 |

^{*} Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination. N/A = Not applicable.

Table 7: Vaccine-Related Systemic Adverse Reactions
Reported in ≥1% of Children Who Received VAQTA* or ProQuad Concomitantly with VAQTA

1 to 14 Days After VAQTA or Vaccination with ProQuad and VAQTA and 1 to 28 Days After Vaccination with ProQuad

| | | á | ING VAQIA | | | | |
|----------------------|---|--|---|------------------------------------|--|--|--|
| Adverse Reactions | | Dose 1 | | Dose 2 | | | |
| | Days | s 1 to 14 | Days 1 to 28 | Day | s 1 to 14 | Days 1 to 28 | |
| | VAQTA [†] (N=1453) (n=1412) % | ProQuad + VAQTA [†] (N=347) (n=328) % | ProQuad + VAQTA (N=347) (n=328) % | VAQTA (N=1301) (n=1254) % | ProQuad + VAQTA [†] (N=292) (n=264) % | ProQuad + VAQTA [†] (N=291) (n=263) % | |
| Fever ^{‡,§} | 5.7 | 14.9 | 15.2 | 4.1 | 8.0 | 8.4 | |
| Irritability | 5.8 | 7.0 | 7.3 | 3.5 | 5.3 | 5.3 | |
| Measles-like rash | 0.0 | 3.4 | 3.4 | 0.0 | 1.1 | 1.1 | |
| Rhinorrhea | 0.6 | 2.7 | 3.0 | 0.6 | 1.1 | 2.7 | |
| Diarrhea | 1.5 | 1.8 | 2.4 | 1.7 | 0.4 | 0.8 | |
| Cough | 0.6 | 2.1 | 2.1 | 0.2 | 0.8 | 1.5 | |
| Vomiting | 1.1 | 0.3 | 0.9 | 0.6 | 0.8 | 1.1 | |

^{*} Systemic adverse events for subjects given VAQTA alone were collected for 14 days postvaccination.

In an open-label clinical trial, 653 children 12 to 23 months of age were randomized to receive a first dose of ProQuad with VAQTA and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or a first dose of ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly and then vaccinated with VAQTA 6 weeks later (N=323). Approximately 6 months later, subjects received either the second doses of ProQuad and VAQTA concomitantly or the second doses of ProQuad and VAQTA separately. The race distribution of the study subjects was as follows: 60.3% White; 21.6% African-American; 9.5% Hispanic; 7.2% other; 1.1% Asian/Pacific; and 0.3% American Indian. The gender distribution of the study subjects was 50.7% male and 49.3% female. Vaccine-related injection-site and systemic adverse reactions observed among recipients of concomitant ProQuad, VAQTA, and pneumococcal 7-valent conjugate vaccine and ProQuad and pneumococcal 7-valent conjugate vaccine at a rate of at least 1% are shown in Tables 8 and 9. In the 28 days after vaccination with the first dose of ProQuad, the rates of fever (including all vaccine- and non-vaccine-related reports) were comparable in subjects who received the 3 vaccines together (38.6%) as compared with subjects given ProQuad and pneumococcal 7-valent conjugate vaccine (42.7%). The rates of fever in the 28 days following the second dose of ProQuad were also comparable in subjects who received ProQuad and VAQTA together (17.4%) as compared with subjects given ProQuad separately from VAQTA (17.0%). In a post-hoc analysis, these differences were not statistically significant after ProQuad (dose 1) (RR 0.90 [95% CI: 0.75, 1.09]) nor after dose 2 (RR

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

[†] Safety follow-up for systemic adverse reactions was 14 days for VAQTA and 28 days for ProQuad + VAQTA.

[‡] Designates a solicited adverse reaction.

[§] Temperature reported as elevated or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

1.02 [95% CI: 0.70, 1.51]). No clinically significant differences in adverse reactions were reported among treatment groups [see Clinical Studies (14)].

Table 8: Vaccine-Related Injection-Site Adverse Reactions

Reported in ≥1% of Children Who Received ProQuad + VAQTA + PCV7* Concomitantly or VAQTA Alone Followed by ProQuad + PCV7 Concomitantly (1 to 5 Days After a Dose of ProQuad)

| Adverse Reactions | | ose 1 | Dos | e 2 |
|------------------------------|---|--|--|--|
| | VAQTA + ProQuad + PCV7 (N=330) (n=311) % | VAQTA Alone Followed by ProQuad + PCV7 (N=323) (n=302) | VAQTA + ProQuad (N=273) (n=265) % | VAQTA Alone Followed by ProQuad (N=240) (n=230) % |
| Injection-Site - ProQuad | | | | |
| Pain/tenderness [†] | 21.2 | 24.2 | 18.1 | 17.0 |
| Erythema [†] | 13.5 | 11.9 | 10.6 | 13.0 |
| Swelling [†] | 7.4 | 10.9 | 8.3 | 11.7 |
| Bruising | 1.9 | 1.3 | 0.8 | 0.4 |
| Injection-Site - VAQTA | | | | |
| Pain/tenderness [†] | 20.6 | 15.3 | 17.5 | 20.3 |
| Erythema [†] | 9.6 | 11.7 | 9.1 | 12.7 |
| Swelling [†] | 6.8 | 9.5 | 6.1 | 7.6 |
| Bruising | 1.3 | 1.1 | 1.1 | 1.6 |
| Rash | 1.0 | 0.0 | 0.4 | 0.4 |
| Injection-Site - PCV7 | | | | |
| Pain/tenderness [†] | 25.4 | 27.6 | N/A | N/A |
| Erythema [†] | 16.4 | 16.6 | N/A | N/A |
| Swelling [†] | 13.2 | 14.3 | N/A | N/A |
| Bruising | 0.6 | 1.7 | N/A | N/A |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

N/A = Not applicable.

Table 9: Vaccine-Related Systemic Adverse Reactions Reported in ≥1% of Children Who Received ProQuad + VAQTA + PCV7* Concomitantly, or VAQTA Alone Followed by ProQuad + PCV7 Concomitantly (1 to 28 Days After a Dose of ProQuad)

| Adverse Reactions | D | ose 1 | Dos | e 2 |
|----------------------------------|---|---|--|--|
| | VAQTA + ProQuad + PCV7 (N=330) (n=311) % | VAQTA Alone Followed by ProQuad + PCV7 (N=323) (n=302) % | VAQTA + ProQuad (N=273) (n=265) % | VAQTA Alone Followed by ProQuad (N=240) (n=230) % |
| Fever ^{†,‡} | 26.4 | 27.2 | 9.1 | 9.6 |
| Irritability | 4.8 | 6.3 | 1.9 | 1.3 |
| Measles-like rash [†] | 2.3 | 4.0 | 0.0 | 0.0 |
| Varicella-like rash [†] | 1.0 | 1.7 | 0.0 | 0.0 |
| Rash (not otherwise specified) | 1.3 | 1.3 | 0.0 | 0.9 |
| Diarrhea | 1.3 | 1.3 | 0.4 | 1.3 |
| Upper respiratory infection | 1.0 | 1.3 | 1.1 | 0.9 |
| Viral infection | 1.0 | 0.7 | 0.0 | 0.0 |
| Rhinorrhea | 0.0 | 0.7 | 1.1 | 0.0 |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

[†] Designates a solicited adverse reaction. Injection-site adverse reactions were solicited only from Days 1 to 5 postvaccination at each vaccine injection site.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

[†] Designates a solicited adverse reaction.

[‡] Temperature reported as elevated or abnormal.

N = number of subjects vaccinated.

n = number of subjects with safety follow-up.

6.2 Post-Marketing Experience

The following adverse events have been identified during post-approval use of either the components of ProQuad or ProQuad. Because the events are in some cases described in the literature or reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Infections and infestations

Subacute sclerosing panencephalitis (see below), encephalitis (see below), aseptic meningitis (see below), meningitis, measles, atypical measles, pneumonia, respiratory infection, infection, varicella (vaccine strain), influenza, herpes zoster, orchitis, epididymitis, cellulitis, skin infection, retinitis, bronchitis, parotitis, sinusitis, impetigo, herpes simplex, candidiasis, rhinitis.

Although not reported following vaccination with ProQuad, cases of encephalitis or meningitis caused by vaccine strain varicella virus have been reported in immunocompetent individuals previously vaccinated with VARIVAX (same varicella vaccine strain as in ProQuad) months to years after vaccination. Reported cases were commonly associated with preceding or concurrent herpes zoster rash (see below).

Blood and the lymphatic system disorders

Aplastic anemia, thrombocytopenia, regional lymphadenopathy, lymphadenitis.

Immune system disorders

Anaphylaxis and related phenomena such as angioneurotic edema, facial edema, and peripheral edema, anaphylactoid reaction.

Psychiatric disorders

Agitation, apathy, nervousness.

Nervous system disorders

Measles inclusion body encephalitis [see Contraindications (4.2)], acute disseminated encephalomyelitis, transverse myelitis, cerebrovascular accident, encephalopathy (see below), Guillain-Barré syndrome, optic neuritis, Bell's palsy, polyneuropathy, ataxia, hypersomnia, afebrile convulsions or seizures, febrile seizure, headache, syncope, dizziness, tremor, paraesthesia.

Eye disorders

Necrotizing retinitis (in immunocompromised individuals), retrobulbar neuritis, ocular palsies, edema of the eyelid, irritation eye.

Ear and labyrinth disorders

Nerve deafness, ear pain.

Vascular disorders

Extravasation blood.

Respiratory, thoracic and mediastinal disorders

Pneumonitis [see Contraindications (4.3)], pulmonary congestion, wheezing, bronchial spasm, epistaxis, sore throat.

Gastrointestinal disorders

Hematochezia, abdominal pain, mouth ulcer.

Skin and subcutaneous tissue disorders

Stevens-Johnson syndrome, Henoch-Schönlein purpura, erythema multiforme, acute hemorrhagic edema of infancy, purpura, skin induration, panniculitis, pruritus.

Musculoskeletal, connective tissue and bone disorders

Arthritis and/or arthralgia (usually transient and rarely chronic, see below); pain of the hip, leg, or neck; myalgia; musculoskeletal pain.

General disorders and administration site conditions

Injection-site complaints (burning and/or stinging of short duration, edema/swelling, hive-like rash, discoloration, hematoma, induration, lump, vesicles, wheal and flare), varicella-like rash, warm to touch, stiffness, warm sensation, inflammation, injection-site hemorrhage, injection-site injury.

Deaths have been reported following vaccination with measles, mumps, and rubella vaccines; however, a causal relationship has not been established in healthy individuals. Death as a direct consequence of disseminated measles vaccine virus infection has been reported in severely immunocompromised individuals in whom a measles-containing vaccine is contraindicated and who were inadvertently vaccinated. However, there were no deaths or permanent sequelae reported in a published

post-marketing surveillance study in Finland involving 1.5 million children and adults who were vaccinated with M-M-R II during 1982 to 1993 {3}.

Encephalitis and encephalopathy have been reported approximately once for every 3 million doses of M-M-R II or measles-, mumps-, and rubella-containing vaccine administered since licensure of these vaccines. The risk of serious neurological disorders following live measles virus vaccine administration remains less than the risk of encephalitis and encephalopathy following infection with wild-type measles (1 per 1000 reported cases) {4,5}.

In severely immunocompromised individuals who have been inadvertently vaccinated with measles-containing vaccine; measles inclusion body encephalitis, pneumonitis, and fatal outcome as a direct consequence of disseminated measles vaccine virus infection have been reported [see Contraindications (4.2)]. In this population, disseminated mumps and rubella vaccine virus infection have also been reported.

Recipients of rubella vaccine may develop chronic joint symptoms. Arthralgia and/or arthritis, and polyneuritis after wild-type rubella virus infection vary in frequency and severity with age and gender, being greatest in adult females and least in pre-pubertal children. Following vaccination in children, reactions in joints are uncommon (0 to 3%) and of brief duration. In women, incidence rates for arthritis and arthralgia are higher than those seen in children (12 to 26%), and the reactions tend to be more marked and of longer duration (e.g., months or years). In adolescent girls, the reactions appear to be intermediate in incidence between those seen in children and adult women.

Chronic arthritis has been associated with wild-type rubella infection and has been related to persistent virus and/or viral antigen isolated from body tissues. Chronic joint symptoms have been reported following administration of rubella-containing vaccine.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of infection with wild-type measles but did receive measles vaccine. Some of these cases may have resulted from unrecognized measles in the first year of life or possibly from the measles vaccination. Based on estimated measles vaccine distribution in the United States (US), the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. The association with wild-type measles virus infection is 6 to 22 cases of SSPE per million cases of measles. The results of a retrospective case-controlled study suggest that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

Cases of aseptic meningitis have been reported to Vaccine Adverse Event Reporting System (VAERS) following measles, mumps, and rubella vaccination. Although a causal relationship between other strains of mumps vaccine and aseptic meningitis has been shown, there is no evidence to link Jeryl Lynn™ mumps vaccine to aseptic meningitis.

Cases of thrombocytopenia have been reported after use of measles vaccine; measles, mumps, and rubella vaccine; and after varicella vaccination. Post-marketing experience with live measles, mumps, and rubella vaccine indicates that individuals with current thrombocytopenia may develop more severe thrombocytopenia following vaccination. In addition, individuals who experienced thrombocytopenia following the first dose of a live measles, mumps, and rubella vaccine may develop thrombocytopenia with repeat doses. Serologic testing for antibody to measles, mumps, or rubella should be considered in order to determine if additional doses of vaccine are needed [see Warnings and Precautions (5.5)].

The reported rate of zoster in recipients of VARIVAX appears not to exceed that previously determined in a population-based study of healthy children who had experienced wild-type varicella {6}. In clinical trials, 8 cases of herpes zoster were reported in 9454 vaccinated individuals 12 months to 12 years of age during 42,556 person-years of follow-up. This resulted in a calculated incidence of at least 18.8 cases per 100,000 person-years. All 8 cases reported after VARIVAX were mild and no sequelae were reported. The long-term effect of VARIVAX on the incidence of herpes zoster is unknown at present.

The vaccine virus (Oka/Merck strain) contained in ProQuad may establish latency of varicella zoster virus in immunocompetent individuals, with the potential for later development of herpes zoster [see Adverse Reactions (6.2), Infections and Infestations].

6.3 Post-Marketing Observational Safety Surveillance Study

Safety was evaluated in an observational study that included 69,237 children vaccinated with ProQuad 12 months to 12 years old. A historical comparison group included 69,237 age-, gender-, and date-of-vaccination (day and month)-matched subjects who were given M-M-R II and VARIVAX concomitantly. The primary objective was to assess the incidence of febrile seizures occurring within

various time intervals after vaccination in 12- to 60-month-old children who had neither been vaccinated against measles, mumps, rubella, or varicella, nor had a history of the wild-type infections (N=31,298 vaccinated with ProQuad, including 31,043 who were 12 to 23 months old). The incidence of febrile seizures was also assessed in a historical control group of children who had received their first vaccination with M-M-R II and VARIVAX concomitantly (N=31,298, including 31,019 who were 12 to 23 months old). The secondary objective was to assess the general safety of ProQuad in the 30-day period after vaccination in children 12 months to 12 years old.

In pre-licensure clinical studies, an increase in fever was observed 5 to 12 days after vaccination with ProQuad (dose 1) compared to M-M-R II and VARIVAX (dose 1) given concomitantly. In the post-marketing observational surveillance study, results from the primary safety analysis revealed an approximate two-fold increase in the risk of febrile seizures in the same 5 to 12 day timeframe after vaccination with ProQuad (dose 1). The incidence of febrile seizures 5 to 12 days after ProQuad (dose 1) (0.70 per 1000 children) was higher than that in children receiving M-M-R II and VARIVAX concomitantly (0.32 per 1000 children) [RR 2.20, 95% confidence interval (CI): 1.04, 4.65]. The incidence of febrile seizures 0 to 30 days after ProQuad (dose 1) (1.41 per 1000 children) was similar to that observed in children receiving M-M-R II and VARIVAX concomitantly [RR 1.10 (95% CI: 0.72, 1.69)]. See Table 10. General safety analyses revealed that the risks of fever (RR=1.89; 95% CI: 1.67, 2.15) and skin eruption (RR=1.68; 95% CI: 1.07, 2.64) were significantly higher after ProQuad (dose 1) compared with those who received concomitant first doses of M-M-R II and VARIVAX, respectively. All medical events that resulted in hospitalization or emergency room visits were compared between the group given ProQuad and the historical comparison group, and no other safety concerns were identified in this study.

Table 10: Confirmed Febrile Seizures Days 5 to 12 and 0 to 30 After Vaccination with ProQuad (dose 1) Compared to Concomitant Vaccination with M-M-R II and VARIVAX (dose 1) in Children 12 to 60 Months of Age

| Time Period | _ | Quad cohort N=31,298) | MMR+V cohort (N=31,298) | | Relative risk (95% CI) |
|--------------|----|--------------------------|----------------------------|-----------------------|------------------------|
| | n | Incidence per 1000 | n | Incidence per 1000 | |
| 5 to 12 Days | 22 | 0.70 | 10 0.32 | | 2.20 (1.04, 4.65) |
| 0 to 30 Days | 44 | 1.41 | 40 | 1.28 | 1.10 (0.72, 1.69) |

In this observational post-marketing study, no case of febrile seizure was observed during the 5 to 12 day postvaccination time period among 26,455 children who received ProQuad as a second dose of M-M-R II and VARIVAX. In addition, detailed general safety data were available from more than 25,000 children who received ProQuad as a second dose of M-M-R II and VARIVAX, most of them (95%) between 4 and 6 years of age, and an analysis of these data by an independent, external safety monitoring committee did not identify any specific safety concern.

7 DRUG INTERACTIONS

7.1 Immune Globulins and Transfusions

Immune globulins (IG) administered concomitantly with ProQuad contain antibodies that may interfere with vaccine virus replication and decrease the expected immune response. Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of IG.

The appropriate suggested interval between transfusion or IG administration and vaccination will vary with the type of transfusion or indication for, and dose of, IG (e.g., 5 months for Varicella Zoster Immune Globulin [VZIG]) {2}. Following administration of ProQuad, any IG including VZIG should not be given for 1 month thereafter unless its use outweighs the benefits of vaccination {2}. [See Warnings and Precautions (5.9).]

7.2 Salicylates

Reye syndrome has been reported following the use of salicylates during wild-type varicella infection. Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with ProQuad. [See Warnings and Precautions (5.10) and Patient Counseling Information (17).]

7.3 Corticosteroids and Immunosuppressive Drugs

ProQuad may be used in individuals who are receiving topical corticosteroids or low-dose corticosteroids for asthma prophylaxis or replacement therapy, e.g., for Addison's disease. ProQuad should not be given to individuals receiving immunosuppressive doses of corticosteroids or other

immunosuppressive drugs. Vaccination with a live, attenuated vaccine, such as varicella or measles, can result in a more extensive vaccine-associated rash or disseminated disease in individuals on immunosuppressive drugs [see Contraindications (4.2)].

7.4 Drug/Laboratory Test Interactions

Live, attenuated measles, mumps, and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be done, it should be administered either any time before, simultaneously with, or at least 4 to 6 weeks after ProQuad.

7.5 Use with Other Vaccines

At least 1 month should elapse between a dose of a measles-containing vaccine such as M-M-R II and a dose of ProQuad, and at least 3 months should elapse between administration of 2 doses of ProQuad or varicella-containing vaccines.

ProQuad may be administered concomitantly with *Haemophilus influenzae* type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant). Additionally, ProQuad may be administered concomitantly with pneumococcal 7-valent conjugate vaccine, and/or hepatitis A (inactivated) vaccines. [See Clinical Studies (14).]

There are no data regarding the administration of ProQuad with inactivated poliovirus vaccine or with other live virus vaccines.

There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed. [See Clinical Studies (14).]

Children under treatment for tuberculosis have not experienced exacerbation of the disease when vaccinated with live measles virus vaccine; no studies have been reported to date of the effect of measles virus vaccines on children with untreated tuberculosis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ProQuad vaccine contains live attenuated measles, mumps, rubella and varicella viruses. The vaccine is contraindicated for use in pregnant women because infection during pregnancy with the wild-type viruses is associated with maternal and fetal adverse outcomes.

For women who are inadvertently vaccinated when pregnant or who become pregnant within 3 months of administration of ProQuad, the healthcare provider should be aware of the following: (1) Reports have indicated that contracting wild-type measles during pregnancy enhances fetal risk. Increased rates of spontaneous abortion, stillbirth, congenital defects, and prematurity have been observed subsequent to infection with wild-type measles during pregnancy. There are no adequate studies of the attenuated (vaccine) strain of measles virus in pregnancy; (2) Mumps infection during the first trimester of pregnancy may increase the rate of spontaneous abortion. Although mumps vaccine virus has been shown to infect the placenta and fetus, there is no evidence that it causes congenital malformations in humans {7}; (3) In a 10-year survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome {8}; and (4) Wild-type varicella, if acquired during pregnancy, can sometimes cause congenital varicella syndrome.

Available data on inadvertent administration of ProQuad to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

There are no relevant animal data.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4%, and 15% to 20%, respectively {9,10}. Data

Human Data

In a 10-year CDC survey involving over 700 pregnant women who received rubella vaccine within 3 months before or after conception (of whom 189 received the Wistar RA 27/3 strain), none of the newborns had abnormalities compatible with congenital rubella syndrome {8}.

8.2 Lactation

Risk Summary

It is not known whether varicella, measles, or mumps vaccine virus is excreted in human milk. Studies have shown that lactating postpartum women vaccinated with live rubella vaccine may secrete the virus in breast milk and transmit it to breastfed infants. {11,12} [See Warnings and Precautions (5.8).]

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ProQuad, and any potential adverse effects on the breastfed child from ProQuad or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Do not administer ProQuad to infants younger than 12 months of age or to children 13 years and older. Safety and effectiveness of ProQuad in infants younger than 12 months of age and in children 13 years and older have not been studied. ProQuad is not approved for use in persons in these age groups. *[See Adverse Reactions (6) and Clinical Studies (14).]*

8.5 Geriatric Use

ProQuad is not indicated for use in the geriatric population (≥age 65).

11 DESCRIPTION

ProQuad (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) is a combined, attenuated, live virus vaccine containing measles, mumps, rubella, and varicella viruses. ProQuad is a sterile lyophilized preparation of (1) the components of M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live): Measles Virus Vaccine Live, a more attenuated line of measles virus, derived from Enders' attenuated Edmonston strain and propagated in chick embryo cell culture; Mumps Virus Vaccine Live, the Jeryl Lynn™ (B level) strain of mumps virus propagated in chick embryo cell culture; Rubella Virus Vaccine Live, the Wistar RA 27/3 strain of live attenuated rubella virus propagated in WI-38 human diploid lung fibroblasts; and (2) Varicella Virus Vaccine Live (Oka/Merck), the Oka/Merck strain of varicella-zoster virus propagated in MRC-5 cells. The cells, virus pools, bovine serum, and recombinant human albumin used in manufacturing are all tested to provide assurance that the final product is free of potential adventitious agents.

ProQuad, when reconstituted as directed, is a sterile suspension for subcutaneous administration. Each 0.5-mL dose contains not less than 3.00 \log_{10} TCID₅₀ of measles virus; 4.30 \log_{10} TCID₅₀ of rubella virus; 3.00 \log_{10} TCID₅₀ of rubella virus; and a minimum of 3.99 \log_{10} PFU of Oka/Merck varicella virus.

Each 0.5-mL dose of the vaccine nominally contains 20 mg of sucrose, 11 mg of hydrolyzed gelatin, 2.5 mg of urea; 2.3 mg of sodium chloride, 16 mg of sorbitol, 0.38 mg of monosodium L-glutamate, 1.4 mg of sodium phosphate, 0.25 mg of recombinant human albumin, 0.13 mg of sodium bicarbonate, 94 mcg of potassium phosphate, 58 mcg of potassium chloride; residual components of MRC-5 cells including DNA and protein; 5 mcg of neomycin, bovine serum albumin (0.5 mcg), and other buffer and media ingredients. The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ProQuad has been shown to induce measles-, mumps-, rubella-, and varicella-specific immunity, which is thought to be the mechanism by which it protects against these four childhood diseases.

The efficacy of ProQuad was established through the use of immunological correlates for protection against measles, mumps, rubella, and varicella. Results from efficacy studies or field effectiveness studies that were previously conducted for the component vaccines were used to define levels of serum antibodies that correlated with protection against measles, mumps, and rubella. Also, in previous studies with varicella vaccine, antibody responses against varicella virus ≥5 gpELISA units/mL in a glycoprotein enzyme-linked immunosorbent assay (gpELISA) (not commercially available) similarly correlated with long-term protection. In these efficacy studies, the clinical endpoint for measles and mumps was a clinical diagnosis of either disease confirmed by a 4-fold or greater rise in serum antibody titers between either postvaccination or acute and convalescent titers; for rubella, a 4-fold or greater rise in antibody titers with or without clinical symptoms of rubella; and for varicella, varicella-like rash that occurred >42 days postvaccination and for which varicella was not excluded by either viral cultures of the lesion or

serological tests. Specific laboratory evidence of varicella either by serology or culture was not required to confirm the diagnosis of varicella. Clinical studies with a single dose of ProQuad have shown that vaccination elicited rates of antibody responses against measles, mumps, and rubella that were similar to those observed after vaccination with a single dose of M-M-R II [see Clinical Studies (14)] and seroresponse rates for varicella virus were similar to those observed after vaccination with a single dose of VARIVAX [see Clinical Studies (14)]. The duration of protection from measles, mumps, rubella, and varicella infections after vaccination with ProQuad is unknown.

12.6 Persistence of Antibody Responses after Vaccination

The persistence of antibody at 1 year after vaccination was evaluated in a subset of 2107 children enrolled in the clinical trials. Antibody was detected in 98.9% (1722/1741) for measles, 96.7% (1676/1733) for mumps, 99.6% (1796/1804) for rubella, and 97.5% (1512/1550) for varicella (≥5 qpELISA units/mL) of vaccinees following a single dose of ProQuad.

Experience with M-M-R II demonstrates that antibodies to measles, mumps, and rubella viruses are still detectable in most individuals 11 to 13 years after primary vaccination {13}. Varicella antibodies were present for up to ten years postvaccination in most of the individuals tested who received 1 dose of VARIVAX.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ProQuad has not been evaluated for its carcinogenic, mutagenic, or teratogenic potential, or its potential to impair fertility.

14 CLINICAL STUDIES

Formal studies to evaluate the clinical efficacy of ProQuad have not been performed.

Efficacy of the measles, mumps, rubella, and varicella components of ProQuad was previously established in a series of clinical studies with the monovalent vaccines. A high degree of protection from infection was demonstrated in these studies {14-21}.

Immunogenicity in Children 12 Months to 6 Years of Age

Prior to licensure, immunogenicity was studied in 7386 healthy children 12 months to 6 years of age with a negative clinical history of measles, mumps, rubella, and varicella who participated in 6 randomized clinical trials. The immunogenicity of ProQuad was similar to that of its individual component vaccines (M-M-R II and VARIVAX), which are currently used in routine vaccination. The immunogenicity of the refrigerator-stable formulation and the frozen formulation of ProQuad were shown to be similar.

The presence of detectable antibody was assessed by an appropriately sensitive enzyme-linked immunosorbent assay (ELISA) for measles, mumps (wild-type and vaccine-type strains), and rubella, and by gpELISA for varicella. For evaluation of vaccine response rates, a positive result in the measles ELISA corresponded to measles antibody concentrations of ≥255 mIU/mL when compared to the WHO II (66/202) Reference Immunoglobulin for Measles.

Children were positive for mumps antibody if the antibody level was ≥10 ELISA units/mL. A positive result in the rubella ELISA corresponded to concentrations of ≥10 IU rubella antibody/mL when compared to the WHO International Reference Serum for Rubella; children with varicella antibody levels ≥5 gpELISA units/mL were considered to be seropositive since a response rate based on ≥5 gpELISA units/mL has been shown to be highly correlated with long-term protection.

Immunogenicity in Children 12 to 23 Months of Age After a Single Dose

In 4 randomized clinical trials, 5446 healthy children 12 to 23 months of age were administered ProQuad, and 2038 children were vaccinated with M-M-R II and VARIVAX given concomitantly at separate injection sites. Subjects enrolled in each of these trials had a negative clinical history, no known recent exposure, and no vaccination history for varicella, measles, mumps, and rubella. Children were excluded from study participation if they had an immune impairment or had a history of allergy to components of the vaccine(s). Except for in 1 trial [see ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine below], no concomitant vaccines were permitted during study participation. The race distribution of the study

subjects across these studies following a first dose of ProQuad was as follows: 66.3% White; 12.7% African-American; 9.9% Hispanic; 6.7% Asian/Pacific; 4.2% other; and 0.2% American Indian. The gender distribution of the study subjects across these studies following a first dose of ProQuad was 52.6% male and 47.4% female. A summary of combined immunogenicity results 6 weeks following administration of a single dose of ProQuad or M-M-R II and VARIVAX is shown in Table 11. These results were similar to the immune response rates induced by concomitant administration of single doses of M-M-R II and VARIVAX at separate injection sites (lower bound of the 95% CI for the risk difference in measles, mumps, and rubella seroconversion rates were >-5.0 percentage points and the lower bound of the 95% CI for the risk difference in varicella seroprotection rates was either >-15 percentage points [one study] or >-10.0 percentage points [three studies]).

Table 11: Summary of Combined Immunogenicity Results 6 Weeks Following the Administration of a Single Dose of ProQuad (Varicella Virus Potency ≥3.97 log₁₀ PFU) or M-M-R II and VARIVAX (Per-Protocol Population)

| Jeuau (varicella virus | | l | Observed | |
|---------------------------------|-----------------------------------|------|---------------------------|----------------------------|
| Group | Antigen | n | Response Rate (95% CI) | Observed GMT (95% CI) |
| ProQuad (N=5446*) | Varicella | 4381 | 91.2% (90.3%, 92.0%) | 15.5 (15.0, 15.9) |
| (1. 0.10) | Measles | 4733 | 97.4% (96.9%, 97.9%) | 3124.9 (3038.9, 3213.3) |
| | Mumps (OD cutoff) [†] | 973 | 98.8% (97.9%, 99.4%) | 105.3 (98.0, 113.1) |
| | Mumps (wild-type ELISA)† | 3735 | 95.8% (95.1%, 96.4%) | 93.1 (90.2, 96.0) |
| | Rubella | 4773 | 98.5% (98.1%, 98.8%) | 91.8 (89.6, 94.1) |
| M-M-R II + VARIVAX (N=2038*) | Varicella | 1417 | 94.1% (92.8%, 95.3%) | 16.6 (15.9, 17.4) |
| , | Measles | 1516 | 98.2% (97.4%, 98.8%) | 2239.6 (2138.3, 2345.6) |
| | Mumps (OD cutoff) [†] | 501 | 99.4% (98.3%, 99.9%) | 87.5 (79.7, 96.0) |
| | Mumps (wild-type ELISA)† | 1017 | 98.0% (97.0%, 98.8%) | 90.8 (86.2, 95.7) |
| | Rubella | 1528 | 98.5% (97.7%, 99.0%) | 102.2 (97.8, 106.7) |

^{*} Includes ProQuad + Placebo followed by ProQuad (Visit 1) (Protocol 009), ProQuad Middle and High Doses (Visit 1) (Protocol 011), ProQuad (Lot 1, Lot 2, Lot 3) (Protocol 012), both the Concomitant and Non-concomitant groups (Protocol 013).

GMT = Geometric mean titer.

ELISA = Enzyme-linked immunosorbent assay.

PFU = Plaque-forming units.

OD = Optical density.

Immunogenicity of the refrigerator-stable formulation of ProQuad (N=1006) was compared with that of the licensed frozen formulation of ProQuad (N=513) for 42 days postvaccination in children 12 through 23 months of age. Statistical analysis of non-inferiority in antibody response rates and GMTs to measles, mumps, rubella, and varicella, at 6 weeks postvaccination is presented in Table 12. The immunogenicity of the refrigerator-stable formulation and the frozen formulation of ProQuad were shown to be similar.

Table 12: Statistical Analysis of Non-Inferiority in Antibody Response Rates and GMTs to Measles, Mumps, Rubella, and VZV, at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or With a VZV Antibody Titer <1.25 gpELISA Units/mL at Baseline Following Vaccination With Refrigerator-Stable ProQuad vs. Frozen

| | Froquad in Children 12 to 25 Months of Age (Fer-Frotocol Analysis) | | | | | | | |
|-------|--|-------|--------------------------------------|----|---------------------------|--------------------------------|--|--|
| | | ProQu | ad (Refrigerator-Stable) (N=1006) | Pı | oQuad (Frozen) (N=513) | Risk Difference (Percentage | | |
| Assay | Parameter | n | Estimated Response* | n | Estimated | Points)*,†/ | | |

[†] The mumps antibody response was assessed by a vaccine-strain ELISA in Protocols 009 and 011 and by a wild-type ELISA in Protocols 012 and 013. In the former assay, the serostatus was based on the OD cutoff of the assay. In the latter assay, 10 mumps ELISA units was used as the serostatus cutoff.

n = Number of per-protocol subjects with evaluable serology.

CI = Confidence interval.

| | | | | | Response* | Fold-Difference*.‡ (95% CI) |
|-----------|----------------|-----|--------|-----|-----------|-----------------------------|
| Measles | % ≥255 mIU/mL | 879 | 99.1% | 452 | 98.5% | 0.6 (-0.5, 2.3) |
| | GMT | | 2412.2 | | 2409.3 | 1.0 (0.9, 1.1) |
| Mumps | % ≥10 Ab Units | 883 | 97.7% | 447 | 98.0% | -0.3 (-1.8, 1.6) |
| | GMT | | 118.7 | | 116.8 | 1.0 (0.9, 1.1) |
| Rubella | % ≥10 IU/mL | 908 | 99.6% | 464 | 99.6% | -0.0 (-0.8, 1.2) |
| | GMT | | 97.1 | | 93.5 | 1.0 (1.0, 1.1) |
| Varicella | % ≥5 gpELISA | 839 | 90.1% | 430 | 88.8% | 1.3 (-2.2, 5.1) |
| | Units/mL | | | | | , |
| | GMT | | 12.3 | | 11.8 | 1.0 (0.9, 1.1) |

^{*} Estimated responses and their risk difference/fold-difference were based on a statistical analysis model adjusting for study centers.

The conclusion of non-inferiority of response rates is based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -5 percentage points for measles, mumps, and rubella response rates and being greater than -10 percentage points for the VZV response rate (*i.e.*, excluding a decrease equal to or more than the pre-specified criterion of either 5 or 10 percentage points). This indicates that the risk difference is statistically significantly less than the pre-specified clinically relevant decrease of 5.0 or 10.0 percentage points at the 1-sided alpha = 0.025 level. The conclusion of non-inferiority of GMTs is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.67 (*i.e.*, excluding a decrease of 1.5-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 1.5-fold difference at the 1-sided alpha = 0.025 level.

N = Number of subjects vaccinated in each treatment group.

ELISA = Enzyme-linked immunosorbent assay.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

CI = Confidence interval; VZV = Varicella-zoster virus.

Immunogenicity in Children 15 to 31 Months of Age After a Second Dose of ProQuad

In 2 of the randomized clinical trials described above {22,23}, a subgroup (N=1035) of the 5446 children administered a single dose of ProQuad were administered a second dose of ProQuad approximately 3 to 9 months after the first dose. Children were excluded from receiving a second dose of ProQuad if they were recently exposed to or developed varicella, measles, mumps, and/or rubella prior to receipt of the second dose. No concomitant vaccines were administered to these children. The race distribution across these studies following a second dose of ProQuad was as follows: 67.3% White; 14.3% African-American; 8.3% Hispanic; 5.4% Asian/Pacific; 4.4% other; 0.2% American Indian; and 0.10% mixed. The gender distribution of the study subjects across these studies following a second dose of ProQuad was 50.4% male and 49.6% female. A summary of immune responses following a second dose of ProQuad is presented in Table 13. Results from this study showed that 2 doses of ProQuad administered at least 3 months apart elicited a positive antibody response to all four antigens in greater than 98% of subjects. The geometric mean titers (GMTs) following the second dose of ProQuad increased approximately 2-fold each for measles, mumps, and rubella, and approximately 41-fold for varicella.

Table 13: Summary of Immune Response to a First and Second Dose of ProQuad in Subjects <3 Years of Age Who Received ProQuad with a Varicella Virus Dose ≥3.97 Log₁₀ PFU*

| | | | Dose 1 N=1097 | | | Dose 2 N=1097 | | |
|---------|--------------------------|-----|------------------------------|----------------------------|-----|---------------------------|----------------------------|--|
| | Serostatus Cutoff/ | | Observed Response Rate | Observed GMT | | Observed Response Rate | Observed GMT | |
| Antigen | Response Criteria | n | (95% CI) | (95% CI) | n | (95% CI) | (95% CI) | |
| Measles | ≥120 mIU/mL [†] | 915 | 98.1% (97.0%, 98.9%) | 2956.8 (2786.3, 3137.7) | 915 | 99.5% (98.7%, 99.8%) | 5958.0 (5518.9, 6432.1) | |
| | ≥255 mIU/mL | 943 | 97.8% (96.6%, 98.6%) | 2966.0 (2793.4, 3149.2) | 943 | 99.4% (98.6%, 99.8%) | 5919.3 (5486.2, 6386.6) | |
| Mumps | ≥OD Cutoff (ELISA | 920 | 98.7% (97.7%, | 106.7 (99.1, 114.8) | 920 | 99.9% (99.4%, 100%) | 253.1 (237.9, 269.2) | |

^{† [}ProQuad (Refrigerator-Stable) – ProQuad (Frozen)].

^{‡ [}ProQuad (Refrigerator-Stable)/ProQuad (Frozen)].

n = Number of subjects with measles antibody titers <255 mIU/mL, mumps antibody titers <10 ELISA Ab Units, rubella antibody titers <10 IU/mL, or VZV antibody titers <1.25 gpELISA units/mL at baseline and with postvaccination serology contributing to the perprotocol analysis.

| | antibody units) | | 99.3%) | | | | |
|-----------|----------------------------------|-----|----------------------------|-------------------|-----|-------------------------|-------------------------|
| Rubella | ≥10 IU/mL | 937 | 97.7% (96.5%, 98.5%) | 91.1 (85.9, 96.6) | 937 | 98.3% (97.2%, 99.0%) | 158.8 (149.1, 169.2) |
| Varicella | <1.25 to ≥5 gpELISA units | 864 | 86.6% (84.1%, 88.8%) | 11.6 (10.9, 12.3) | 864 | 99.4% (98.7%, 99.8%) | 477.5 (437.8, 520.7) |
| | ≥OD Cutoff (gpELISA units) | 695 | 87.2% (84.5%, 89.6%) | 11.6 (10.9, 12.4) | 695 | 99.4% (98.5%, 99.8%) | 478.7 (434.8, 527.1) |

* Includes the following treatment groups: ProQuad + Placebo followed by ProQuad (Visit 1) (Protocol 009) and ProQuad (Middle and High Dose) (Protocol 011).

† Samples from Protocols 009 and 011 were assayed in the legacy format Measles ELISA, which reported antibody titers in Measles ELISA units. To convert titers from ELISA units to mIU/mL, titers for these 2 protocols were divided by 0.1025. The lowest measurable titer postvaccination is 207.5 mIU/mL. The response rate for measles in the legacy format is the percent of subjects with a negative baseline measles antibody titer, as defined by the optical density (OD) cutoff, with a postvaccination measles antibody titer ≥207.5 mIU/mL.

Samples from Protocols 009 and 011 were assayed in the legacy format Rubella ELISA, which reported antibody titers in Rubella ELISA units. To convert titers from ELISA units to IU/mL, titers for these 2 protocols were divided by 1.28.

ProQuad (Middle Dose) = ProQuad containing a varicella virus dose of 3.97 log₁₀ PFU.

ProQuad (High Dose) = ProQuad containing a varicella virus dose of 4.25 log₁₀ PFU.

ELISA = Enzyme-linked immunosorbent assay.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

N = Number vaccinated at baseline.

n = Number of subjects who were per-protocol Postdose 1 and Postdose 2 and satisfied the given prevaccination serostatus cutoff.

CI = Confidence interval.

GMT = Geometric mean titer.

PFU = Plaque-forming units.

Immunogenicity in Children 4 to 6 Years of Age Who Received a First Dose of ProQuad After Primary Vaccination With M-M-R II and VARIVAX

In a clinical trial, 799 healthy 4- to 6-year-old children who had received M-M-R II and VARIVAX at least 1 month prior to study entry were randomized to receive ProQuad and placebo (N=399), M-M-R II and placebo concomitantly at separate injection sites (N=205), or M-M-R II and VARIVAX concomitantly at separate injection sites (N=195). Children were eligible if they were previously administered primary doses of M-M-R II and VARIVAX, either concomitantly or non-concomitantly, at 12 months of age or older. Children were excluded if they were recently exposed to measles, mumps, rubella, and/or varicella, had an immune impairment, or had a history of allergy to components of the vaccine(s). No concomitant vaccines were permitted during study participation. [See Adverse Reactions (6.1) for ethnicity and gender information.]

A summary of antibody responses to measles, mumps, rubella, and varicella at 6 weeks postvaccination in subjects who had previously received M-M-R II and VARIVAX is shown in Table 14. Results from this study showed that a first dose of ProQuad after primary vaccination with M-M-R II and VARIVAX elicited a positive antibody response to all four antigens in greater than 98% of subjects. Postvaccination GMTs for recipients of ProQuad were similar to those following a second dose of M-M-R II and VARIVAX administered concomitantly at separate injection sites (the lower bound of the 95% CI around the fold difference in measles, mumps, rubella, and varicella GMTs excluded 0.5). Additionally, GMTs for measles, mumps, and rubella were similar to those following a second dose of M-M-R II given concomitantly with placebo (the lower bound of the 95% CI around the fold difference for the comparison of measles, mumps, and rubella GMTs excluded 0.5).

Table 14: Summary of Antibody Responses to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination in Subjects 4 to 6 Years of Age Who Had Previously Received M-M-R II and VARIVAX (Per-Protocol Population)

| Group Number | | GMT (95% CI) | Seropositivity Rate | % ≥4-Fold Rise in Titer (95% CI) | Geometric Mean Fold Rise (95% CI) |
|-----------------|-----|-----------------|---------------------|---|--|
| (Description) | n | , | Measles | * | , |
| Group 1 (N=399) | 367 | 1985.9 | 100% | 4.9% | 1.21 |

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| (ProQuad + placebo) | | (1817.6, 2169.9) | (99.0%, 100%) | (2.9%, 7.6%) | (1.13, 1.30) |
|---|-----|------------------|----------------|----------------|----------------|
| Group 2 (N=205) | 185 | 2046.9 | 100% | 4.3% | 1.28 |
| (M-M-R II + placebo) | | (1815.2, 2308.2) | (98.0%, 100%) | (1.9%, 8.3%) | (1.17, 1.40) |
| Group 3 (N=195) | 171 | 2084.3 | 99.4% | 4.7% | 1.31 |
| (M-M-R II + VARIVAX) | | (1852.3, 2345.5) | (96.8%, 100%) | (2.0%, 9.0%) | (1.17, 1.46) |
| | | | Mumps | | |
| Group 1 (N=399) | 367 | 206.0 | 99.5% | 27.2% | 2.43 |
| (ProQuad + placebo) | | (188.2, 225.4) | (98.0%, 99.9%) | (22.8%, 32.1%) | (2.19, 2.69) |
| Group 2 (N=205) | 185 | 308.5 | 100% | 41.1% | 3.69 |
| (M-M-R II + placebo) | | (269.6, 352.9) | (98.0%, 100%) | (33.9%, 48.5%) | (3.14, 4.32) |
| Group 3 (N=195) | 171 | 295.9 | 100% | 41.5% | 3.36 |
| (M-M-R II + VARIVAX) | | (262.5, 333.5) | (97.9%, 100%) | (34.0%, 49.3%) | (2.84, 3.97) |
| | | | Rubella | ‡ | |
| Group 1 (N=399) | 367 | 217.3 | 100% | 32.7% | 3.00 |
| (ProQuad + placebo) | | (200.1, 236.0) | (99.0%, 100%) | (27.9%, 37.8%) | (2.72, 3.31) |
| Group 2 (N=205) | 185 | 174.0 | 100% | 31.9% | 2.81 |
| (M-M-R II + placebo) | | (157.3, 192.6) | (98.0%, 100%) | (25.2%, 39.1%) | (2.41, 3.27) |
| Group 3 (N=195) | 171 | 154.1 | 99.4% | 26.9% | 2.47 |
| (M-M-R II + VARIVAX) | | (138.9, 170.9) | (96.8%, 100%) | (20.4%, 34.2%) | (2.17, 2.81) |
| | | | Varicella | \$ | |
| Group 1 (N=399) | 367 | 322.2 | 98.9% | 80.7% | 12.43 |
| (ProQuad + placebo) | | (278.9, 372.2) | (97.2%, 99.7%) | (76.2%, 84.6%) | (10.63, 14.53) |
| Group 2 (N=205) | 185 | N/A | N/A | N/A | N/A |
| (M-M-R II + placebo) | 171 | 200.2 | 00.40/ | 71.00/ | 9.50 |
| Group 3 (N=195) (M-M-R II + VARIVAX) | 171 | 209.3 | 99.4% | 71.9% | 8.50 |
| (INI-INI-K II + VAKIVAX) | | (171.2, 255.9) | (96.8%, 100%) | (64.6%, 78.5%) | (6.69, 10.81) |

^{*} Measles GMTs are reported in mIU/mL; seropositivity corresponds to ≥120 mIU/mL.

Immunogenicity Following Concomitant Use with Other Vaccines

ProQuad with Pneumococcal 7-valent Conjugate Vaccine and/or VAQTA

In a clinical trial, 1027 healthy children 12 to 15 months of age were randomized to receive ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly (N=510) at separate injection sites or ProQuad and pneumococcal 7-valent conjugate vaccine non-concomitantly (N=517) at separate clinic visits. [See Adverse Reactions (6.1) for ethnicity and gender information.] The statistical analysis of non-inferiority in antibody response rates to measles, mumps, rubella, and varicella at 6 weeks postvaccination for subjects are shown in Table 15. In the per-protocol population, seroconversion rates were not inferior in children given ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly when compared to seroconversion rates seen in children given these vaccines non-concomitantly for measles, mumps, and rubella. In children with baseline varicella antibody titers <1.25 gpELISA units/mL, the varicella seroprotection rates were not inferior when rates after concomitant and non-concomitant vaccination were compared 6 weeks postvaccination. Statistical analysis of non-inferiority in GMTs to S. pneumoniae serotypes at 6 weeks postvaccination are shown in Table 16. Geometric mean antibody titers (GMTs) for S. pneumoniae types 4, 6B, 9V, 14, 18C, 19F, and 23F were not inferior when antibody titers in the concomitant and non-concomitant groups were compared 6 weeks postvaccination.

Table 15: Statistical Analysis of Non-Inferiority in Antibody Response Rates to Measles, Mumps, Rubella, and Varicella at 6 Weeks Postvaccination for Subjects Initially Seronegative to Measles, Mumps, or Rubella, or With Varicella Antibody Titer <1.25 gpELISA units at Baseline in the ProQuad + PCV7* Treatment Group and the ProQuad Followed by PCV7 Control Group (Per-Protocol Analysis)

[†] Mumps GMTs are reported in mumps Ab units/mL; seropositivity corresponds to ≥10 Ab units/mL.

[‡] Rubella titers obtained by the legacy format were converted to their corresponding titers in the modified format. Rubella serostatus was determined after the conversion to IU/mL: seropositivity corresponds to ≥10 IU/mL.

[§] Varicella GMTs are reported in gpELISA units/mL; seropositivity rate is reported by % of subjects with postvaccination antibody titers ≥5 gpELISA units/mL. Percentages are calculated as the number of subjects who met the criterion divided by the number of subjects contributing to the per-protocol analysis.

gpELISA = Glycoprotein enzyme-linked immunosorbent assay; ELISA = Enzyme-linked immunosorbent assay; CI = Confidence interval; GMT = Geometric mean titer; N/A = Not applicable; N = Number of subjects vaccinated; n = number of subjects in the per-protocol analysis.

| | Pro | ProQuad + PCV7 (N=510) | | uad followed by PCV7 (N=259) | Difference |
|------------------------------------|-----|------------------------------------|-----------------------------------|------------------------------------|--|
| Assay Parameter | n | Estimated Response [†] | Estimated n Response [†] | | (percentage points) ^{†,‡} (95% CI) |
| Measles % ≥255 mIU/mL | 406 | 97.3% | 204 | 99.5% | -2.2 (-4.6, 0.2) |
| Mumps % ≥10 Ab units/mL | 403 | 96.6% | 208 | 98.6% | -1.9 (-4.5, 1.0) |
| Rubella % ≥10 IU/mL | 377 | 98.7% | 195 | 97.9% | 0.9 (-1.3, 4.1) |
| Varicella % ≥5 gpELISA units/mL | 379 | 92.5% | 192 | 87.9% | 4.5 (-0.4, 10.4) |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

Ab = antibody; ELISA = Enzyme-linked immunosorbent assay; gpELISA = Glycoprotein enzyme-linked immunosorbent assay; CI = Confidence interval.

Table 16: Statistical Analysis of Non-Inferiority in GMTs to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination in the ProQuad + PCV7* Treatment Group and the PCV7 Followed by ProQuad Control Group (Per-Protocol Analysis)

| | | Group 1 ProQuad + PCV7 (N=510) | | Group 2 PCV7 followed by ProQuad (N=258) | | |
|----------|-----------|--------------------------------------|-----|--|------------------------------------|--------------------------------|
| Serotype | Parameter | Estimated n Response [†] | | n | Estimated Response [†] | Fold-Difference*,‡ (95% CI) |
| 4 | GMT | 410 | 1.5 | 193 | 1.3 | 1.2 (1.0, 1.4) |
| 6B | GMT | 410 | 8.9 | 192 | 8.4 | 1.1 (0.9, 1.2) |
| 9V | GMT | 409 | 2.9 | 193 | 2.5 | 1.2 (1.0, 1.3) |
| 14 | GMT | 408 | 6.5 | 193 | 5.7 | 1.1 (1.0, 1.3) |
| 18C | GMT | 408 | 2.3 | 193 | 2.0 | 1.2 (1.0, 1.3) |
| 19F | GMT | 408 | 3.5 | 192 | 3.1 | 1.1 (1.0, 1.3) |
| 23F | GMT | 413 | 4.1 | 197 | 3.7 | 1.1 (1.0, 1.3) |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

In a clinical trial, 653 healthy children 12 to 15 months of age were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly (N=330) or ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later (N=323). [See Adverse Reactions (6.1) for ethnicity and gender information.] Statistical analysis of non-inferiority of the response rate for varicella antibody at 6 weeks postvaccination among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 17. For the varicella component of ProQuad, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥5 gpELISA units/mL 6 weeks after their first dose of ProQuad was non-inferior when ProQuad was administered with VAQTA and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥5 gpELISA units/mL when ProQuad was

Seronegative defined as baseline measles antibody titer <255 mIU/mL for measles, baseline mumps antibody titer <10 ELISA Ab units/mL for mumps, and baseline rubella antibody titer <10 IU/mL for rubella.

[†] Estimated responses and their differences were based on statistical analysis models adjusting for study center.

[‡] ProQuad + PCV7 - ProQuad followed by PCV7.

The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.*, excluding a decrease equal to or more than the prespecified criterion of 10.0 percentage points). This indicates that the difference is statistically significantly less than the prespecified clinically relevant decrease of 10.0 percentage points at the 1-sided alpha = 0.025 level.

N = Number of subjects vaccinated in each treatment group.

n = Number of subjects with measles antibody titer <255 mIU/mL, mumps antibody titer <10 ELISA Ab units/mL, rubella antibody titer <10 IU/mL, or varicella antibody titer <1.25 gpELISA units/mL at baseline and with postvaccination serology contributing to the per-protocol analysis.

[†] Estimated responses and their fold-difference were based on statistical analysis models adjusting for study center and prevaccination titer.

[‡] ProQuad + PCV7 / PCV7 followed by ProQuad.

The conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5, (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference is statistically significantly less than the pre-specified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.

N = Number of subjects vaccinated in each treatment group; n = Number of subjects contributing to the per-protocol analysis for the given serotype; GMT = geometric mean titer; CI = Confidence interval.

administered with pneumococcal 7-valent conjugate vaccine alone. Statistical analysis of non-inferiority of the seropositivity rate for hepatitis A antibody at 4 weeks postdose 2 of VAQTA among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 18. The seropositivity rate to hepatitis A 4 weeks after a second dose of VAQTA given concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine (defined as the percent of subjects with a titer ≥10 mIU/mL) was non-inferior to the seropositivity rate observed when VAQTA was administered separately from ProQuad and pneumococcal 7-valent conjugate vaccine. Statistical analysis of non-inferiority in GMT to S. pneumoniae serotypes at 6 weeks postvaccination among subjects who received VAQTA concomitantly or non-concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine is shown in Table 19. Additionally, the GMTs for S. pneumoniae types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad and VAQTA were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent conjugate vaccine with ProQuad alone. An earlier clinical study involving 617 healthy children provided data that indicated that the seroresponse rates 6 weeks post vaccination for measles, mumps, and rubella in those given M-M-R II and VAQTA concomitantly (N=309) were non-inferior as compared to historical controls.

Table 17: Statistical Analysis of Non-Inferiority of the Response Rate for Varicella Antibody at 6 Weeks Postvaccination Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)

| | | p 1: Concomitant VAQTA with ProQuad + PCV7 (N=330) | | up 2: Non-concomitant A separate from ProQuad + PCV7 (N=323) | Difference [†] (percentage points): Group 1 – Group 2 | |
|---------------------------------------|------|---|------|--|---|--|
| Parameter | n | Estimated Response [†] | n | Estimated Response [†] | (95% CI) | |
| % ≥5 gpELISA units/mL [‡] | 225§ | 93.2% | 232§ | 98.3% | -5.1 (-9.3, -1.4) | |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

The conclusion of similarity (non-inferiority) was based on the lower bound of the 2-sided 95% CI on the risk difference excluding a decrease of 10 percentage points or more (lower bound >-10.0). This indicated that the risk difference was statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

Table 18: Statistical Analysis of Non-Inferiority of the Seropositivity Rate (SPR) for Hepatitis A Antibody at 4 Weeks Postdose 2 of VAQTA Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7* (Per-Protocol Analysis Set)

| | Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330) | | Group 2: Non- concomitant VAQTA separate from ProQuad + PCV7 (N=323) | | Difference [†] |
|---------------------------|---|------------------------------------|--|------------------------------------|---|
| Parameter | n | Estimated Response [†] | n | Estimated Response [†] | (percentage points): Group 1 - Group 2 (95% CI) |
| % ≥10 mIU/mL [‡] | 182 [§] | 100.0% | 159 [§] | 99.3% | 0.7 (-1.4, 3.8) |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the risk difference being greater than -10 percentage points (*i.e.*, excluding a decrease of 10 percentage points or more) (lower bound >-10.0). This indicated that the risk difference was

N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for varicella; CI = Confidence interval.

[†] Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.

[‡] 6 weeks following Dose 1.

[§] Initial Serostatus <1.25 gpELISA units/ mL.

CI = Confidence interval; N = Number of subjects enrolled/randomized; <math>n = Number of subjects contributing to the per-protocol analysis for hepatitis A.

[†] Estimated responses and their differences were based on a statistical analysis model adjusting for combined study center.

[‡] 4 weeks following receipt of 2 doses of VAQTA.

[§] Regardless of initial serostatus.

statistically significantly greater than the pre-specified clinically relevant difference of -10 percentage points at the 1-sided alpha = 0.025 level.

Table 19: Statistical Analysis of Non-Inferiority in Geometric Mean Titers (GMT) to *S. pneumoniae* Serotypes at 6 Weeks Postvaccination Among Subjects Who Received VAQTA Concomitantly or Non-Concomitantly With ProQuad and PCV7*

(Per-Protocol Analysis Set)

| (i ci i i otocci Analysis ect) | | | | | | | |
|--------------------------------|--|------------------------------------|-----|--|--|--|--|
| | Group 1: Concomitant VAQTA with ProQuad + PCV7 (N=330) | | VAQ | Group 2: n-concomitant IA separate from oQuad + PCV7 (N=323) | | | |
| Serotype | n | Estimated Response [†] | n | Estimated Response [†] | Fold-Difference [†] (95% CI) | | |
| 4 | 246 | 1.9 | 247 | 1.7 | 1.1 (0.9, 1.3) | | |
| 6B | 246 | 9.9 | 246 | 9.9 | 1.0 (0.8, 1.2) | | |
| 9V | 247 | 3.7 | 247 | 4.2 | 0.9 (0.8, 1.0) | | |
| 14 | 248 | 7.8 | 247 | 7.6 | 1.0 (0.9, 1.2) | | |
| 18C | 247 | 2.9 | 247 | 2.7 | 1.1 (0.9, 1.3) | | |
| 19F | 248 | 4.0 | 248 | 3.8 | 1.1 (0.9, 1.2) | | |
| 23F | 247 | 5.1 | 247 | 4.4 | 1.1 (1.0, 1.3) | | |

^{*} PCV7 = Pneumococcal 7-valent conjugate vaccine.

The conclusion of non-inferiority was based on the lower bound of the 2-sided 95% CI on the fold-difference being greater than 0.5 (*i.e.*, excluding a decrease of 2-fold or more). This indicates that the fold-difference was statistically significantly less than the prespecified clinically relevant 2-fold difference at the 1-sided alpha = 0.025 level.

ProQuad Administered with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) and Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine

In a clinical trial, 1913 healthy children 12 to 15 months of age were randomized to receive ProQuad plus diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP) and Haemophilus influenzae type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine concomitantly at separate injection sites (N=949), ProQuad at the initial visit followed by DTaP and Haemophilus b conjugate and hepatitis B (recombinant) vaccine given concomitantly 6 weeks later (N=485), or M-M-R II and VARIVAX given concomitantly at separate injection sites (N=479) at the first visit. [See Adverse Reactions (6.1) for ethnicity and gender information.] Seroconversion rates and antibody titers for measles, mumps, rubella, varicella, anti-PRP, and hepatitis B were comparable between the 2 groups given ProQuad at approximately 6 weeks postvaccination indicating that ProQuad and Haemophilus b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine may be administered concomitantly at separate injection sites (see Table 20 below). Response rates for measles, mumps, rubella, varicella, Haemophilus influenzae type b, and hepatitis B were not inferior in children given ProQuad plus Haemophilus influenzae type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines concomitantly when compared to ProQuad at the initial visit and Haemophilus influenzae type b conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccines given concomitantly 6 weeks later. There are insufficient data to support concomitant vaccination with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (data not shown).

Table 20: Summary of the Comparison of the Immunogenicity Endpoints for Measles, Mumps, Rubella, Varicella, Haemophilus influenzae type b, and Hepatitis B Responses Following Vaccination with ProQuad, Haemophilus influenzae type b Conjugate (Meningococcal Protein Conjugate), and Hepatitis B (Recombinant) Vaccine and DTaP Administered Concomitantly Versus Non-Concomitant Vaccination with ProQuad Followed by These Vaccines

| Concomitant Group | Non- Concomitant | |
|----------------------|---------------------|--|
| | Group | |

CI = Confidence interval; GMT = Geometric mean titer; N = Number of subjects enrolled/randomized; n = Number of subjects contributing to the per-protocol analysis for *S. pneumoniae* serotypes.

[†] Estimated responses and their fold-difference were based on statistical analysis models adjusting for combined study center and prevaccination titer.

| | | N=949 | N=485 | | |
|--------------------|----------------------------|----------|----------|--------------------------------|----------------------------------|
| Vaccine Antigen | Parameter | Response | Response | Risk Difference (95% CI) | Criterion for Non-inferiority |
| Measles | % ≥120 mIU/mL | 97.8% | 98.7% | -0.9 (-2.3, 0.6) | LB >-5.0 |
| Mumps | % ≥10 ELISA Ab units/mL | 95.4% | 95.1% | 0.3 (-1.7, 2.6) | LB >-5.0 |
| Rubella | % ≥10 IU/mL | 98.6% | 99.3% | -0.7 (-1.8, 0.5) | LB >-5.0 |
| Varicella | % ≥5 gpELISA units/mL | 89.6% | 90.8% | -1.2 (-4.1, 2.0) | LB >-10.0 |
| HiB-PRP | % ≥1.0 mcg/mL | 94.6% | 96.5% | -1.9 (-4.1, 0.8) | LB >-10.0 |
| HepB | % ≥10 mIU/mL | 95.9% | 98.8% | -2.8 (-4.8, -0.8) | LB >10.0 |

HiB-PRP = Haemophilus influenzae type b, polyribosyl phosphate; HepB = hepatitis B; LB = lower bound, limit for non-inferiority comparison.

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16 HOW SUPPLIED/STORAGE AND HANDLING

No. 4103 — ProQuad is supplied as follows:

- (1) a package of 10 single-dose vials of lyophilized vaccine, NDC 0006-4103-00 (package A)
- (2) a separate package of 10 vials of sterile water diluent (package B).

Storage

During shipment, to ensure that there is no loss of potency, the vaccine must be maintained at a temperature of 2° to 8°C (36° to 46°F) or colder, but not exceed temperatures lower than -50°C (-58°F). Use of dry ice may subject ProQuad to temperatures colder than -50°C (-58°F).

Vaccine vial

Before reconstitution, store the lyophilized vaccine in a refrigerator at 2° to 8°C (36° to 46°F) or colder. The lyophilized vaccine may also be stored in a freezer and subsequently transferred to a refrigerator; however, the lyophilized vaccine should not be refrozen.

DO NOT STORE LYOPHILIZED VACCINE AT ROOM TEMPERATURE.

IF LYOPHILIZED VACCINE IS INADVERTENTLY STORED AT ROOM TEMPERATURE, IT SHOULD BE DISCARDED.

Protect the vaccine from light at all times since such exposure may inactivate the vaccine viruses.

IF NOT USED IMMEDIATELY, THE RECONSTITUTED VACCINE MAY BE STORED AT ROOM TEMPERATURE, PROTECTED FROM LIGHT, FOR UP TO 30 MINUTES.

DISCARD RECONSTITUTED VACCINE IF IT IS NOT USED WITHIN 30 MINUTES.

Diluent vial

Diluent should be stored separately at room temperature (68° to 77°F, 20° to 25°C), or in a refrigerator (36° to 46°F, 2° to 8°C).

For information regarding stability under conditions other than those recommended, call 1-800-MERCK-90.

17 PATIENT COUNSELING INFORMATION

Instructions

Provide the required vaccine information to the patient, parent, or guardian.

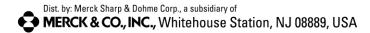
Inform the patient, parent, or guardian of the benefits and risks associated with vaccination.

Inform the patient, parent, or guardian that the vaccine recipient should avoid use of salicylates for 6 weeks after vaccination with ProQuad [see Warnings and Precautions (5.10) and Drug Interactions (7.2)].

Instruct postpubertal females to avoid pregnancy for 3 months following vaccination [see Indications and Usage (1), Contraindications (4.4) and Use in Specific Populations (8.1)].

Inform patients, parents, or guardians that vaccination with ProQuad may not offer 100% protection from measles, mumps, rubella, and varicella infection.

Instruct patients, parents, or guardians to report any adverse reactions to their health care provider. The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967, or report online at http://www.vaers.hhs.gov.



For patent information: www.merck.com/product/patent/home.html

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EXHIBIT 252

Case 2:20-cv-02470-WBS-JDP Document 9 Filed 12/29/20 Page 401 of 497 WARNINGS AND PRECAUTIONS-

These highlights do not include all the information needed to use FLUARIX QUADRIVALENT safely and effectively. See full prescribing information for FLUARIX QUADRIVALENT.

FLUARIX QUADRIVALENT (Influenza Vaccine) injectable suspension, for intramuscular use 2019-2020 Formula

Initial U.S. Approval: 2012

----INDICATIONS AND USAGE-

FLUARIX QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLUARIX QUADRIVALENT is approved for use in persons aged 6 months and older. (1)

------DOSAGE AND ADMINISTRATION ----------For intramuscular injection only. (2)

| Age | Vaccination Status | Dose and Schedule |
|-------------------|------------------------------|-----------------------------|
| 6 months through | Not previously vaccinated | Two doses (0.5-mL |
| 8 years | with influenza vaccine | each) at least 4 weeks |
| | | apart (2.1) |
| | Vaccinated with influenza | One or 2 doses ^a |
| | vaccine in a previous season | (0.5-mL each) (2.1) |
| 9 years and older | Not applicable | One 0.5-mL dose (2.1) |

^a One dose or 2 doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If 2 doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

--- DOSAGE FORMS AND STRENGTHS--

Suspension for injection supplied in 0.5-mL single-dose prefilled syringes. (3)

---CONTRAINDICATIONS --

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. (4, 11)

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUARIX QUADRIVALENT should be based on careful consideration of potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUARIX QUADRIVALENT. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

-ADVERSE REACTIONS-

- In adults, the most common (≥10%) solicited local adverse reaction was pain (36%); the most common systemic adverse reactions were muscle aches (16%), headache (16%), and fatigue (16%). (6.1)
- In children aged 6 through 35 months, the most common (≥10%) solicited local adverse reactions were pain (17%) and redness (13%); the most common systemic adverse reactions were irritability (16%), loss of appetite (14%), and drowsiness (13%). (6.1)
- In children aged 3 through 17 years, the solicited local adverse reactions were pain (44%), redness (23%), and swelling (19%). (6.1)
- In children aged 3 through 5 years, the most common (≥10%) systemic adverse reactions were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse reactions were fatigue (20%), muscle aches (18%), headache (16%), arthralgia (10%), and gastrointestinal symptoms (10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Glax oS mith Kline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

--- USE IN SPECIFIC POPULATIONS-

Geriatric Use: Antibody responses were lower in geriatric subjects who received FLUARIX QUADRIVALENT than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/20xx

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLUARIX QUADRIVALENT is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine [see Description (11)]. FLUARIX QUADRIVALENT is approved for use in persons aged 6 months and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

The dose and schedule for FLUARIX QUADRIVALENT are presented in Table 1.

Table 1. FLUARIX QUADRIVALENT: Dosing

| Age | Vaccination Status | Dose and Schedule |
|--------------------------|--------------------------------|---|
| 6 months through 8 years | Not previously vaccinated with | Two doses (0.5-mL each) at least |
| | influenza vaccine | 4 weeks apart |
| | Vaccinated with influenza | One or 2 doses ^a (0.5-mL each) |
| | vaccine in a previous season | |
| 9 years and older | Not applicable | One 0.5-mL dose |

^a One dose or 2 doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of seasonal influenza with vaccines. If 2 doses, administer each 0.5-mL dose at least 4 weeks apart.

2.2 Administration Instructions

Shake well before administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Attach a sterile needle to the prefilled syringe and administer intramuscularly.

The preferred sites for intramuscular injection are the anterolateral thigh for children aged 6 through 11 months and the deltoid muscle of the upper arm for persons aged 12 months and older if muscle mass is adequate. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously, intradermally, or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLUARIX QUADRIVALENT is a suspension for injection. Each 0.5-mL dose is supplied in single-dose prefilled TIP-LOK syringes.

4 CONTRAINDICATIONS

Do not administer FLUARIX QUADRIVALENT to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous administration of any influenza vaccine [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLUARIX QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an increased frequency of GBS. Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is inconclusive. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLUARIX QUADRIVALENT. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of FLUARIX QUADRIVALENT.

5.4 Altered Immunocompetence

If FLUARIX QUADRIVALENT is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent persons.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLUARIX QUADRIVALENT may not protect all susceptible individuals.

5.6 Persons at Risk of Bleeding

As with other intramuscular injections, FLUARIX QUADRIVALENT should be given with caution in individuals with bleeding disorders, such as hemophilia or on anticoagulant therapy, to avoid the risk of hematoma following the injection.

6 ADVERSE REACTIONS

The safety experience with FLUARIX (trivalent influenza vaccine) is relevant to FLUARIX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions [see Description (11)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of FLUARIX QUADRIVALENT could reveal adverse reactions not observed in clinical trials.

In adults who received FLUARIX QUADRIVALENT, the most common (\geq 10%) solicited local adverse reaction was pain (36%). The most common (\geq 10%) systemic adverse reactions were muscle aches (16%), headache (16%), and fatigue (16%).

In children aged 6 through 35 months who received FLUARIX QUADRIVALENT, the most common (\geq 10%) solicited local adverse reactions were pain (17%) and redness (13%). The most common (\geq 10%) systemic adverse reactions were irritability (16%), loss of appetite (14%), and drowsiness (13%). In children aged 3 through 17 years who received FLUARIX QUADRIVALENT, solicited local adverse reactions were pain (44%), redness (23%), and swelling (19%). In children aged 3 through 5 years, the most common (\geq 10%) systemic adverse reactions were drowsiness (17%), irritability (17%), and loss of appetite (16%); in children aged 6 through 17 years, the most common systemic adverse reactions were fatigue (20%), muscle aches (18%), headache (16%), arthralgia (10%), and gastrointestinal symptoms (10%).

FLUARIX QUADRIVALENT in Adults

Trial 1 (NCT01204671) was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled, safety, and immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 3,036) or one of 2 formulations of comparator trivalent influenza vaccine (FLUARIX; TIV-1, n = 1,010; or TIV-2, n = 610), each containing an influenza type B virus that corresponded to one of the 2 type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 18 years and older (mean age: 58 years) and 57% were female; 69% were white, 27% were Asian, and 4% were of other racial/ethnic groups. Solicited events were collected for 7 days (day of vaccination and the next 6 days). The frequencies of solicited adverse reactions are shown in Table 2.

Table 2. FLUARIX QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a of Vaccination in Adults^b (Total Vaccinated Cohort)

| reactions within 7 Days of | FLUA QUADRIY | ARIX | Trival TI | V-1 | za Vaccine (TIV) TIV-2 | | |
|--|-----------------|----------------------|-----------------|-----------------------------|------------------------|-----------------------------|--|
| | n = 3,01 | | (B VIC n = 1 | toria) ^d .003 | - | nagata) ^e 607 | |
| | 9/ | <i>^</i> | | ⁄o | | % | |
| Adverse Reaction | Any | Grade 3 ^f | Any | Grade 3 ^f | Any | Grade 3 ^f | |
| Local | | | | | | | |
| Pain | 36 | 0.8 | 37 | 1 | 31 | 0.5 | |
| Redness | 2 | 0 | 2 | 0 | 2 | 0 | |
| Swelling | 2 | 0 | 2 | 0 | 1 | 0 | |
| Systemic | | | | | | | |
| Muscle aches | 16 | 0.5 | 19 | 0.8 | 16 | 0.5 | |
| Headache | 16 | 0.9 | 16 | 0.8 | 13 | 0.7 | |
| Fatigue | 16 | 0.7 | 18 | 0.6 | 15 | 0.5 | |
| Arthralgia | 8 | 0.5 | 10 | 0.7 | 9 | 0.3 | |
| Gastrointestinal symptoms ^g | 7 0.4 | | 7 | 0.2 | 6 | 0.3 | |
| Shivering | 4 | 0.4 | 5 | 0.3 | 4 | 0.2 | |
| Fever ^h | 2 | 0 | 1 | 0 | 2 | 0 | |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

Grade 3 redness, swelling: Defined as >100 mm.

Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.

Grade 3 fever: Defined as >102.2°F (39.0°C).

- g Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.
- h Fever: Defined as \geq 99.5°F (37.5°C).

n = Number of subjects with diary card completed.

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 1: NCT01204671.

^c Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

^d Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

^e Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza type B virus of Yamagata lineage.

f Grade 3 pain: Defined as significant pain at rest; prevented normal everyday activities.

Unsolicited events occurring within 21 days of vaccination (Day 0 to 20) were reported in 13%, 14%, and 15% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively. The unsolicited adverse reactions that occurred most frequently (≥0.1% for FLUARIX QUADRIVALENT) included dizziness, injection site hematoma, injection site pruritus, and rash. Serious adverse events occurring within 21 days of vaccination were reported in 0.5%, 0.6%, and 0.2% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively.

FLUARIX QUADRIVALENT in Children

Trial 7 (NCT01439360) was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the efficacy of FLUARIX QUADRIVALENT. In this trial, subjects aged 6 through 35 months received FLUARIX QUADRIVALENT (n = 6,006) or a control vaccine (n = 6,012). The comparator was pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.) in children younger than 12 months, HAVRIX (Hepatitis A Vaccine) in children 12 months and older with a history of influenza vaccination, or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) in those with no history of influenza vaccination. Subjects were aged 6 through 35 months, and one child aged 43 months (mean age: 22 months); 51% were male; 27% were white, 45% were Asian, and 28% were of other racial/ethnic groups. Children aged 12 months and older with no history of influenza vaccination and children younger than 12 months received 2 doses of FLUARIX QUADRIVALENT or the control vaccine approximately 28 days apart. Children aged 12 months and older with a history of influenza vaccination received one dose. Solicited local adverse reactions and systemic adverse events were collected using diary cards for 7 days (day of vaccination and the next 6 days). The incidences of solicited adverse reactions are shown in Table 3.

Table 3. FLUARIX QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a after First Vaccination in Children Aged 6 through 35 Months^b (Total

Vaccinated Cohort)

| | FLUARIX QUADRIVALENT % | | _ | | | enza Active parator ^{c,d} % |
|--------------------|------------------------|----------------------|-----|----------------------|--|--|
| Adverse Reaction | Any | Grade 3 ^e | Any | Grade 3 ^e | | |
| Local | n = | 5,899 | n = | 5,896 | | |
| Pain | 17 | 0.4 | 18 | 0.5 | | |
| Redness | 13 | 0 | 14 | 0 | | |
| Swelling | 8 | 0 | 9 | 0 | | |
| Systemic | n = | 5,898 | n = | 5,896 | | |
| Irritability | 16 | 0.7 | 18 | 1 | | |
| Loss of appetite | 14 | 1 | 15 | 1 | | |
| Drowsiness | 13 | 0.7 | 14 | 0.9 | | |
| Fever ^f | 6 | 1 | 7 | 1 | | |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = Number of subjects with diary card completed.

Grade 3 swelling, redness: Defined as >50 mm.

Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.

Grade 3 loss of appetite: Defined as not eating at all.

Grade 3 drowsiness: Defined as prevented normal activity.

Grade 3 fever: Defined as >102.2°F (39.0°C).

In children who received a second dose of FLUARIX QUADRIVALENT or the Non-Influenza Active Comparator vaccine, the incidences of solicited adverse reactions following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 44% and 45% of subjects who received FLUARIX QUADRIVALENT (n = 6,006) and the comparator vaccine (n = 6,012), respectively. Serious adverse events (SAEs) occurring during the study period (6 to 8

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 7: NCT01439360.

^c Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).

^d Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithK line Biologicals) (Dose 2) for those with no history of influenza vaccination.

^e Grade 3 pain: Defined as cried when limb was moved/spontaneously painful.

f Fever: Defined as ≥100.4°F (38.0°C).

months) were reported in 3.6% of subjects who received FLUARIX QUADRIVALENT and in 3.3% of subjects who received the comparator vaccine.

Trial 2 (NCT01196988) was a randomized, double-blind, active-controlled, safety, and immunogenicity trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 915) or one of 2 formulations of comparator trivalent influenza vaccine (FLUARIX; TIV-1, n = 912; or TIV-2, n = 911), each containing an influenza type B virus that corresponded to one of the 2 type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). Subjects were aged 3 through 17 years and 52% were male; 56% were white, 29% were Asian, 12% were black, and 3% were of other racial/ethnic groups. Children aged 3 through 8 years with no history of influenza vaccination received 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of influenza vaccination and children aged 9 years and older received one dose. Solicited local adverse reactions and systemic adverse events were collected using diary cards for 7 days (day of vaccination and the next 6 days). The frequencies of solicited adverse reactions are shown in Table 4.

Table 4. FLUARIX QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a after First Vaccination in Children Aged 3 through 17 Years^b (Total

Vaccinated Cohort)

| vaccinated Conorty | | | Triv | alent Influe | nza Vaccine | (TIV) | |
|--------------------|-----|---------------------|-------------|---------------------------|-------------|----------------------|--|
| | FLU | ARIX | | V-1 | | (V-2 | |
| | | VALENT ^c | | (B Victoria) ^d | | nagata) ^e | |
| | _ | ⁄o | ` | % | * | % | |
| | Any | Grade 3f | Any | Grade 3 ^f | Any | Grade 3f | |
| Adverse Reaction | | A | ged 3 thro | ugh 17 Yea | rs | | |
| Local | n = | 903 | n = | 901 | n = | 905 | |
| Paing | 44 | 2 | 42 | 2 | 40 | 0.8 | |
| Redness | 23 | 1 | 21 | 0.2 | 21 | 0.7 | |
| Swelling | 19 | 0.8 | 17 | 1 | 15 | 0.2 | |
| | | 1 | Aged 3 thro | Aged 3 through 5 Years | | | |
| Systemic | n = | 291 | n = 314 | | n = 279 | | |
| Drowsiness | 17 | 1 | 12 | 0.3 | 14 | 0.7 | |
| Irritability | 17 | 0.7 | 13 | 0.3 | 14 | 0.7 | |
| Loss of appetite | 16 | 0.3 | 8 | 0 | 10 | 0.7 | |
| Feverh | 9 | 0.3 | 9 | 0.3 | 8 | 1 | |
| | | A | ged 6 thro | ugh 17 Yea | rs | | |
| Systemic | n = | 613 | n = | 588 | n = | 626 | |
| Fatigue | 20 | 2 | 19 | 1 | 16 | 0.5 | |
| Muscle aches | 18 | 0.7 | 16 | 1 | 16 | 0.5 | |
| Headache | 16 | 1 | 19 | 0.7 | 15 | 0.6 | |
| Arthralgia | 10 | 0.3 | 9 | 0.7 | 7 | 0.2 | |
| Gastrointestinal | 10 | 1 | 10 | 0.7 | 7 | 0.3 | |
| symptomsi | | | | | | | |
| Shivering | 6 | 0.5 | 4 | 0.5 | 5 | 0 | |
| Fever ^h | 6 | 1 | 9 | 0.5 | 6 | 0.3 | |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = Number of subjects with diary card completed.

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 2: NCT01196988.

^c Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

^d Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

^e Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza type B virus of Yamagata lineage.

- f Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <6 years), or significant pain at rest, prevented normal everyday activities (children ≥6 years).
 - Grade 3 redness, swelling: Defined as >50 mm.
 - Grade 3 drowsiness: Defined as prevented normal activity.
- Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.
- Grade 3 loss of appetite: Defined as not eating at all.
- Grade 3 fever: Defined as >102.2°F (39.0°C).
- Grade 3 fatigue, muscle aches, headache, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.
- g Percentage of subjects with any pain by age subgroup: 39%, 38%, and 37% for FLUARIX QUADRIVALENT, TIV-1, and TIV-2, respectively, in children aged 3 through 8 years and 52%, 50%, and 46% for FLUARIX QUADRIVALENT, TIV-1, and TIV-2, respectively, in children aged 9 through 17 years.
- h Fever: Defined as ≥ 99.5 °F (37.5°C).
- ¹ Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

In children who received a second dose of FLUARIX QUADRIVALENT, TIV-1, or TIV-2, the incidences of adverse reactions following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of any vaccination were reported in 31%, 33%, and 34% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively. The unsolicited adverse reactions that occurred most frequently (≥0.1% for FLUARIX QUADRIVALENT) included injection site pruritus and rash. Serious adverse events occurring within 28 days of any vaccination were reported in 0.1%, 0.1%, and 0.1% of subjects who received FLUARIX QUADRIVALENT, TIV-1, or TIV-2, respectively.

FLUARIX (Trivalent Formulation)

FLUARIX has been administered to 10,317 adults aged 18 through 64 years, 606 subjects aged 65 years and older, and 2,115 children aged 6 months through 17 years in clinical trials. The incidence of solicited adverse reactions in each age-group is shown in Tables 5 and 6.

Table 5. FLUARIX (Trivalent Formulation): Incidence of Solicited Local and Systemic Adverse Reactions within 4 Days^a of Vaccination in Adults (Total Vaccinated Cohort)

| | • | Trial | l 3 ^b | Ì | Trial 4 ^c | | | | |
|--------------|-----|----------------------|------------------|-----------------------|----------------------|---|--------------|----------------------|--|
| | A | ged 18 throu | ıgh 64 Y | ears | I | Aged 65 Yea | rs and Older | | |
| Adverse | n = | JARIX = 760 % | | lace bo = 192 % | | FLUARIX Comparato n = 601-602 n = 596 % % | | - | |
| Reaction | Any | Grade 3 ^d | Any | Grade 3 ^d | Any | Grade 3 ^d | Any | Grade 3 ^d | |
| Local | | | | | | | | | |
| Pain | 55 | 0.1 | 12 | 0 | 19 | 0 | 18 | 0 | |
| Redness | 18 | 0 | 10 | 0 | 11 | 0.2 | 13 | 0.7 | |
| Swelling | 9 | 0.1 | 6 | 0 | 6 | 0 | 9 | 0.7 | |
| Syste mic | | | | | | | | | |
| Muscle aches | 23 | 0.4 | 12 | 0.5 | 7 | 0.3 | 7 | 0 | |
| Fatigue | 20 | 0.4 | 18 | 1 | 9 | 0.3 | 10 | 0.7 | |
| Headache | 19 | 0.1 | 21 | 1 | 8 | 0.3 | 8 | 0.3 | |
| Arthralgia | 6 | 0.1 | 6 | 0.5 | 6 | 0.5 | 5 | 0.2 | |
| Shivering | 3 | 0.1 | 3 | 0 | 2 | 0.2 | 2 | 0 | |
| Fevere | 2 | 0 | 2 | 0 | 2 | 0 | 0.5 | 0 | |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = Number of subjects with diary card completed.

Grade 3 redness, swelling: Defined as >50 mm.

Grade 3 fever: Defined as >102.2°F (39.0°C).

^a Four days included day of vaccination and the subsequent 3 days.

^b Trial 3 was a randomized, double-blind, placebo-controlled, safety, and immunogenicity trial (NCT00100399).

^c Trial 4 was a randomized, single-blind, active-controlled, safety, and immunogenicity trial (NCT00197288). The active control was FLUZONE, a U.S.-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur Inc.).

^d Grade 3 pain, muscle aches, fatigue, headache, arthralgia, shivering: Defined as prevented normal activity.

^e Fever: Defined as ≥100.4°F (38.0°C) in Trial 3, and ≥99.5°F (37.5°C) in Trial 4.

Table 6. FLUARIX (Trivalent Formulation): Incidence of Solicited Local and Systemic Adverse Reactions within 4 Days^a of First Vaccination in Children Aged 3 through 17 Years^b (Total

Vaccinated Cohort)

| | | Aged 3 through 4 Years | | Aged 5 through 17 Years | | | | |
|--------------------|-----|------------------------|-----|-------------------------|----------------------|----------------------|-----------------------|----------------------|
| | | UARIX = 350 | | nparator = 341 | FLUARIX n = 1,348 | | Comparator n = 451 | |
| Adverse | _ | % | • | % | <u> </u> | % G 1 26 | | % 1 26 |
| Reaction | Any | Grade 3 ^c | Any | Grade 3 ^c | Any | Grade 3 ^c | Any | Grade 3 ^c |
| Local | 1 | 1 | | • | | 1 | 1 | 1 |
| Pain | 35 | 2 | 38 | 1 | 56 | 0.8 | 56 | 0.7 |
| Redness | 23 | 0.3 | 20 | 0 | 18 | 1 | 16 | 0.7 |
| Swelling | 14 | 0 | 13 | 0 | 14 | 2 | 13 | 0.7 |
| Systemic | | | | | | | | |
| Irritability | 21 | 0.9 | 22 | 0 | - | _ | _ | _ |
| Loss of appetite | 13 | 0.9 | 15 | 0.9 | | _ | _ | _ |
| Drowsiness | 13 | 0.6 | 20 | 0.9 | _ | _ | _ | _ |
| Fever ^d | 7 | 1 | 8 | 2 | 4 | 0.3 | 3 | 0.2 |
| Muscle aches | _ | _ | | _ | 29 | 0.4 | 29 | 0.4 |
| Fatigue | | _ | ļ | _ | 20 | 1 | 19 | 1 |
| Headache | _ | _ | _ | _ | 15 | 0.5 | 16 | 0.9 |
| Arthralgia | | _ | _ | _ | 6 | 0.1 | 6 | 0.2 |
| Shivering | | _ | _ | _ | 3 | 0.1 | 4 | 0.2 |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available.

Grade 3 swelling, redness: Defined as >50 mm.

Grade 3 fever: Defined as >102.2°F (39.0°C).

In children who received a second dose of FLUARIX or the comparator vaccine, the incidences of adverse reactions following the second dose were similar to those observed after the first dose.

Serious Adverse Reactions: In the 4 clinical trials in adults (N = 10,923), there was a single case of anaphylaxis within one day following administration of FLUARIX (<0.01%).

n = Number of subjects with diary card completed.

^a Four days included day of vaccination and the subsequent 3 days.

^b Trial 6 was a single-blind, active-controlled, safety, and immunogenicity U.S. trial (NCT00383123). The active control was FLUZONE, a U.S.-licensed trivalent, inactivated influenza vaccine (Sanofi Pasteur Inc.).

^c Grade 3 pain, irritability, loss of appetite, drowsiness, muscle aches, fatigue, headache, arthralgia, shivering: Defined as prevented normal activity.

^d Fever: Defined as ≥99.5°F (37.5°C).

FLUARIX QUADRIVALENT Concomitant Administration with Zoster Vaccine Recombinant, Adjuvanted (SHINGRIX)

In an open-label, randomized trial (NCT 01954251), adults aged 50 years and older (median 63 years, range 50 to 92 years) received FLUARIX QUADRIVALENT and SHINGRIX at Month 0 and SHINGRIX at Month 2 (n = 413), or FLUARIX QUADRIVALENT at Month 0 and SHINGRIX at Months 2 and 4 (n = 415). Information about solicited local and systemic adverse reactions was collected using diary cards for 7 days (day of vaccination and the next 6 days). The rates of the solicited, systemic adverse reactions of fatigue, headache, myalgia, shivering, and fever (≥37.5°C) reported in subjects receiving FLUARIX QUADRIVALENT and SHINGRIX concomitantly were similar to those observed with SHINGRIX alone, and higher than when FLUARIX QUADRIVALENT was given alone.

6.2 Postmarketing Experience

Beyond those events reported above in the clinical trials for FLUARIX QUADRIVALENT or FLUARIX, the following adverse reactions have been identified during post-approval use of FLUARIX QUADRIVALENT or FLUARIX (trivalent influenza vaccine). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and Lymphatic System Disorders

Lymphadenopathy.

Cardiac Disorders

Tachycardia.

Ear and Labyrinth Disorders

Vertigo.

Eye Disorders

Conjunctivitis, eye irritation, eye pain, eye redness, eye swelling, eyelid swelling.

Gastrointestinal Disorders

Abdominal pain or discomfort, swelling of the mouth, throat, and/or tongue.

General Disorders and Administration Site Conditions

Asthenia, chest pain, influenza-like illness, feeling hot, injection site mass, injection site reaction, injection site warmth, body aches.

Immune System Disorders

Anaphylactic reaction including shock, anaphylactoid reaction, hypersensitivity, serum sickness.

Infections and Infestations

Injection site abscess, injection site cellulitis, pharyngitis, rhinitis, tonsillitis.

Nervous System Disorders

Convulsion, encephalomyelitis, facial palsy, facial paresis, Guillain-Barré syndrome, hypoesthesia, myelitis, neuropathy, paresthesia, syncope.

Respiratory, Thoracic, and Mediastinal Disorders

Asthma, bronchospasm, dyspnea, respiratory distress, stridor.

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema multiforme, facial swelling, pruritus, Stevens-Johnson syndrome, sweating, urticaria.

Vascular Disorders

Henoch-Schönlein purpura, vasculitis.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

In an open-label trial (NCT 01954251), FLUARIX QUADRIVALENT was administered concomitantly with Zoster Vaccine Recombinant, Adjuvanted (SHINGRIX) [see Adverse Reactions (6.1), Clinical Studies (14.4)].

7.2 Immunos uppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater-than-physiologic doses), may reduce the immune response to FLUARIX QUADRIVALENT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLUARIX QUADRIVALENT during pregnancy. Healthcare providers are encouraged to register women by calling 1-888-452-9622.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are insufficient data on FLUARIX QUADRIVALENT in pregnant women to inform vaccine-associated risks.

A developmental toxicity study was performed in female rats administered FLUARIX QUADRIVALENT prior to mating and during gestation and lactation periods. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). This study revealed no adverse effects on fetal or preweaning development due to FLUARIX QUADRIVALENT (see Data).

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal influenza are at increased risk of severe illness associated with influenza infection compared with non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: In a developmental toxicity study, female rats were administered FLUARIX QUADRIVALENT by intramuscular injection 4 and 2 weeks prior to mating, on Gestation Days 3, 8, 11, and 15, and on Lactation Day 7. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to Postnatal Day 25 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether FLUARIX QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of FLUARIX QUADRIVALENT on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLUARIX QUADRIVALENT and any potential adverse effects on the breastfed child from FLUARIX QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of FLUARIX QUADRIVALENT in children younger than 6 months have not been established.

Safety and effectiveness of FLUARIX QUADRIVALENT in individuals aged 6 months through 17 years have been established [see Adverse Reactions (6.1), Clinical Studies (14.3)].

8.5 Geriatric Use

In a randomized, double-blind (2 arms) and open-label (one arm), active-controlled trial, immunogenicity and safety were evaluated in a cohort of subjects aged 65 years and older who received FLUARIX QUADRIVALENT (n = 1,517); 469 of these subjects were aged 75 years and older. In subjects aged 65 years and older, the geometric mean antibody titers (GMTs) post-vaccination and seroconversion rates were lower than in younger subjects (aged 18 through 64 years) and the frequencies of solicited and unsolicited adverse reactions were generally lower than in younger subjects.

11 DESCRIPTION

FLUARIX QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a sterile, colorless, and slightly opalescent suspension. FLUARIX QUADRIVALENT is prepared from influenza viruses propagated in embryonated chicken eggs. Each of the influenza viruses is produced and purified separately. After harvesting the virus-containing fluids, each influenza virus is concentrated and purified by zonal centrifugation using a linear sucrose density gradient solution containing detergent to disrupt the viruses. Following dilution, the vaccine is further purified by diafiltration. Each influenza virus solution is inactivated by the consecutive effects of sodium deoxycholate and formaldehyde leading to the production of a "split virus." Each split inactivated virus is then suspended in sodium phosphate-buffered isotonic sodium chloride solution. Each vaccine is formulated from the split inactivated virus solutions.

FLUARIX QUADRIVALENT has been standardized according to U.S. Public Health Service (USPHS) requirements for the 2019-2020 influenza season and is formulated to contain 60 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose, in the recommended ratio of 15 mcg HA of each of the following 4 influenza virus strains (2 A strains and 2 B strains): A/Brisbane/02/2018 (H1N1) pdm09 (IVR-190), A/Kansas/14/2017 (H3N2) NYMC X-327, B/Maryland/15/2016 NYMC BX-69A (a B/Colorado/06/2017-like virus), and B/Phuket/3073/2013.

FLUARIX QUADRIVALENT is formulated without preservatives. FLUARIX QUADRIVALENT does not contain thimerosal. Each 0.5-mL dose also contains octoxynol-10 (TRITON X-100) \leq 0.115 mg, α -tocopheryl hydrogen succinate \leq 0.135 mg, and polysorbate 80 (Tween 80) \leq 0.550 mg. Each dose may also contain residual amounts of hydrocortisone \leq 0.0015 mcg, gentamicin sulfate \leq 0.15 mcg, ovalbumin \leq 0.050 mcg, formaldehyde \leq 5 mcg, and sodium deoxycholate \leq 65 mcg from the manufacturing process.

The tip caps and plungers of the prefilled syringes of FLUARIX QUADRIVALENT are not made with natural rubber latex

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

Public health authorities give annual influenza vaccine composition recommendations. Inactivated influenza vaccines are standardized to contain the hemagglutinins of influenza viruses representing the virus types or subtypes likely to circulate in the United States during the influenza season. Two influenza type B virus lineages (Victoria and Yamagata) are of public health importance because they have co-circulated since 2001. FLUARIX (trivalent influenza vaccine) contains 2 influenza A subtype viruses and one influenza type B virus.

Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HI

antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects. 1,2 Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual replacement of one or more influenza viruses in each year's influenza vaccine.

Annual revaccination is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLUARIX QUADRIVALENT has not been evaluated for carcinogenic or mutagenic potential or male infertility in animals. Vaccination of female rats with FLUARIX QUADRIVALENT had no effect on fertility [see Use in Specific Populations (8.1)].

14 CLINICAL STUDIES

14.1 Efficacy against Influenza

The efficacy experience with FLUARIX is relevant to FLUARIX QUADRIVALENT because both vaccines are manufactured using the same process and have overlapping compositions [see Description (11)].

The efficacy of FLUARIX was evaluated in a randomized, double-blind, placebo-controlled trial conducted in 2 European countries during the 2006-2007 influenza season. Efficacy of FLUARIX, containing A/New Caledonia/20/1999 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 influenza virus strains, was defined as the prevention of culture-confirmed influenza A and/or B cases, for vaccine antigenically matched strains, compared with placebo. Healthy subjects aged 18 through 64 years (mean age: 40 years) were randomized (2:1) to receive FLUARIX (n = 5,103) or placebo (n = 2,549) and monitored for influenza-like illnesses (ILI) starting 2 weeks post-vaccination and lasting for approximately 7 months. In the overall population, 60% of subjects were female and 99.9% were white. Culture-confirmed influenza was assessed by active and passive surveillance of ILI. Influenza-like illness was defined as at least one general symptom (fever ≥100°F and/or myalgia) and at least one respiratory symptom (cough and/or sore throat). After an episode of ILI, nose and throat swab samples were collected for analysis; attack rates and vaccine efficacy were calculated (Table 7).

Table 7. FLUARIX (Trivalent Formulation): Attack Rates and Vaccine Efficacy against Culture-Confirmed Influenza A and/or B in Adults (Total Vaccinated Cohort)

| | | | Attack Rates (n/N) | | Vaccine Effica | acy |
|---------------|-------------|---------------------|--------------------|-------------------|-------------------|-------------|
| | N | n | % | % | Lower Limit | Upper Limit |
| Antigenically | Matched St | trains ^a | | | | |
| FLUARIX | 5,103 | 49 | 1.0 | 66.9b | 51.9 | 77.4 |
| Placebo | 2,549 | 74 | 2.9 | _ | - | _ |
| All Culture-C | Confirmed I | nfluenza (M | atched, Unmatched | l, and Unty | ped) ^c | |
| FLUARIX | 5,103 | 63 | 1.2 | 61.6 ^b | 46.0 | 72.8 |
| Placebo | 2,549 | 82 | 3.2 | _ | _ | _ |

^a There were no vaccine matched culture-confirmed cases of A/New Caledonia/20/1999 (H1N1) or B/Malaysia/2506/2004 influenza virus strains with FLUARIX or placebo.

In a post-hoc exploratory analysis by age, vaccine efficacy (against culture-confirmed influenza A and/or B cases, for vaccine antigenically matched strains) in subjects aged 18 through 49 years was 73.4% (95% CI: 59.3, 82.8) (number of influenza cases: FLUARIX [n = 35/3,602] and placebo [n = 66/1,810]). In subjects aged 50 through 64 years, vaccine efficacy was 13.8% (95% CI: -137.0, 66.3) (number of influenza cases: FLUARIX [n = 14/1,501] and placebo [n = 8/739]). As the trial lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

The efficacy of FLUARIX QUADRIVALENT was evaluated in Trial 7, a randomized, observer-blind, non-influenza vaccine-controlled trial conducted in 13 countries in Asia, Europe, and Central America during the 2011-2012 and 2012-2013 Northern Hemisphere influenza seasons, and from 2012 to 2014 during influenza seasons in subtropical countries. Healthy subjects aged 6 through 35 months (mean age: 22 months) were randomized (1:1) to receive FLUARIX QUADRIVALENT (n = 6,006) or a non-influenza control vaccine (n = 6,012). In the overall population, 51% were male; 27% were white, 45% were Asian, and 28% were of other racial/ethnic groups. Children aged 12 months and older with no history of influenza vaccination and children younger than 12 months received 2 doses of FLUARIX QUADRIVALENT or the Non-Influenza Active Comparator vaccine approximately 28 days apart. Children aged 12 months and older with a history of influenza vaccination received one dose.

The influenza virus strain composition of FLUARIX QUADRIVALENT administered in each of the 5 study cohorts followed the World Health Organization (WHO) recommendations (which included 2nd B strain from 2012 onwards) for each influenza season associated with a particular cohort.

Efficacy of FLUARIX QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-confirmed influenza A and/or B disease, due to any seasonal

^b Vaccine efficacy for FLUARIX exceeded a pre-defined threshold of 35% for the lower limit of the 2-sided 95% Confidence Interval (CI).

^c Of the 22 additional cases, 18 were unmatched and 4 were untyped; 15 of the 22 cases were A (H3N2) (11 cases with FLUARIX and 4 cases with placebo).

influenza strain, compared with non-influenza control vaccines. Influenza disease included episodes of influenza-like illness (ILI, i.e., fever ≥100.4°F with any of the following: cough, runny nose, nasal congestion, or breathing difficulty) or a consequence of influenza virus infection (acute otitis media or lower respiratory illnesses). Among subjects with RT-PCR-positive influenza A and/or B disease, subjects were further prospectively classified based on the presence of adverse outcomes associated with influenza infection: fever >102.2°F, physician-diagnosed acute otitis media, physician-diagnosed lower respiratory tract illness, physician-diagnosed serious extra-pulmonary complications, hospitalization in the intensive care unit, or supplemental oxygen required for more than 8 hours. Subjects were monitored for influenza disease by passive and active surveillance starting 2 weeks post-vaccination and lasting for approximately 6 months. After an episode of ILI, lower respiratory illness, or acute otitis media, nasal swabs were collected and tested for influenza A and/or B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture and by antigenic characterization to determine whether the viral strains matched those in the vaccine. Vaccine efficacy for subjects with RT-PCR confirmed and culture-confirmed vaccine matching strains (According-to-Protocol (ATP) cohort for efficacy – time to event) is presented in Table 8.

Table 8. Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children Aged 6

through 35 Months^a (ATP Cohort for Efficacy – Time to Event)

| through 25 Months (1111 Cono | | | Time to Eventy | | | | |
|--|---|----------------|-----------------------|------------------|-------------------|-------------|--|
| | | | Attack Rates (n/N) | Vaccine Efficacy | | | |
| | N^b | n ^c | % | % | Lower Limit | Upper Limit | |
| All RT-PCR-Confirmed Influe | nza | | | | | | |
| FLUARIX QUADRIVALENT | 5,707 | 344 | 6.03 | 49.8 | 41.8 ^d | 56.8 | |
| Non-Influenza Comparator ^{e, f} | 5,697 | 662 | 11.62 | - | - | - | |
| All Culture-Confirmed Influen | za | | | | | | |
| FLUARIX QUADRIVALENT | 5,707 | 303 | 5.31 | 51.2 | 44.1g | 57.6 | |
| Non-Influenza Comparator ^{e, f} | 5,697 | 602 | 10.57 | ı | - | - | |
| All Antigenically Matched Cul- | All Antigenically Matched Culture-Confirmed Influenza | | | | | | |
| FLUARIX QUADRIVALENT | 5,707 | 88 | 1.54 | 60.1 | 49.1 ^h | 69.0 | |
| Non-Influenza Comparator ^{e, f} | 5,697 | 216 | 3.79 | - | _ | - | |

ATP = According-to-Protocol; RT-PCR = Reverse Transcriptase Polymerase Chain Reaction.

- ^e Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).
- f Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.
- g Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion of >10% for the lower limit of the 2-sided 95% CI.
- ^h Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion of >15% for the lower limit of the 2-sided 95% CI.

The vaccine efficacy against RT-PCR-confirmed influenza associated with adverse outcomes was 64.6% (97.5% CI 53.2%, 73.5%). The vaccine efficacy against RT-PCR-confirmed influenza associated with adverse outcomes due to A/H1N1, A/H3N2, B/Victoria, and B/Yamagata was 71.4% (95% CI 48.5%, 85.2%), 51.3% (95% CI 32.7%, 65.2%), 86.7% (95% CI 52.8%, 97.9%), and 68.9% (95% CI 50.6%, 81.2%), respectively.

For RT-PCR-confirmed influenza cases associated with adverse outcomes, the incidence of the specified adverse outcomes is presented in Table 9.

^a Trial 7: NCT01439360.

^b Number of subjects in the ATP cohort for efficacy – time to event, which included subjects who met all eligibility criteria, who were followed for efficacy and complied with the study protocol until the influenza-like episode.

^c Number of subjects who reported at least one case in the reporting period.

^d Vaccine efficacy for FLUARIX QUADRIVALENT met the pre-defined criterion for the lower limit of the 2-sided 97.5% CI (>15% for all influenza).

Table 9. Incidence of Adverse Outcomes Associated with RT-PCR-Positive Influenza in Children

Aged 6 through 35 Months^a (ATP Cohort for Efficacy- Time to Event)^b

| Aged o through 55 Wionths" (| Non-Influenza Active | | | | | | | |
|--|----------------------|--------------------------------|----------|-----------|---------------------------------------|-----|--|--|
| | FLUARIX | FLUARIX QUADRIVALENT n = 5,707 | | | Comparator ^{c,d} $n = 5,697$ | | | |
| Influenza-Associated | Number | Number of | 0./ | Number | Number of | 0./ | | |
| Symptome | of Events | Subjects f | <u>%</u> | of Events | Subjects f | % | | |
| Fever >102.2°F/39°C | 62 | 61 | 1.1 | 184 | 183 | 3.2 | | |
| Acute otitis media (AOM) ^g | 5 | 5 | 0.1 | 15 | 15 | 0.3 | | |
| Physician-diagnosed lower respiratory tract illness ^h | 28 | 28 | 0.5 | 62 | 61 | 1.1 | | |
| Physician-diagnosed serious extra-pulmonary complications ⁱ | 2 | 2 | 0 | 3 | 3 | 0.1 | | |
| Hospitalization in the intensive care unit | 0 | 0 | 0 | 0 | 0 | 0 | | |
| Supplemental oxygen required for more than 8 hours | 0 | 0 | 0 | 0 | 0 | 0 | | |

ATP = According-to-Protocol; RT-PCR = Reverse transcriptase polymerase chain reaction.

- ^c Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).
- ^d Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.
- ^e Subjects who experienced more than one adverse outcome, each outcome was counted in the respective category.
- f Number of subjects with at least one event in a given category.
- g Analyses considered AOM cases confirmed by otoscopy.
- ^h Pneumonia, lower respiratory tract infection, bronchiolitis, bronchitis, or croup infection as per final diagnosis by physician.
- ⁱ Includes myositis, encephalitis or other neurologic condition including seizure, myocarditis/pericarditis or other serious medical condition as per final diagnosis by physician.

a Trial 7: NCT01439360.

^b Number of subjects in the ATP cohort for efficacy – time to event, which included subjects who met all eligibility criteria, who were followed for efficacy and complied with the study protocol until the influenza-like episode.

14.2 Immunological Evaluation of FLUARIX QUADRIVALENT in Adults

Trial 1 was a randomized, double-blind (2 arms) and open-label (one arm), active-controlled, safety, immunogenicity, and non-inferiority trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 1,809) or one of 2 formulations of comparator trivalent influenza vaccine (FLUARIX, TIV-1, n = 608 or TIV-2, n = 534), each containing an influenza type B virus that corresponded to one of the 2 type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). Subjects aged 18 years and older (mean age: 58 years) were evaluated for immune responses to each of the vaccine antigens 21 days following vaccination. In the overall population, 57% of subjects were female; 69% were white, 27% were Asian, and 4% were of other racial/ethnic groups.

The immunogenicity endpoints were GMTs of serum HI antibodies adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI antibody titer over baseline to ≥1:40 following vaccination, performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results were available after vaccination. FLUARIX QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [TIV/FLUARIX QUADRIVALENT] ≤1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLUARIX QUADRIVALENT ≤10%). The antibody response to influenza B strains contained in FLUARIX QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 10).

Table 10. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 21 Days after

Vaccination in Adults (ATP Cohort for Immunogenicity)

| | | Trivalent Influenza Vaccine (TIV) | | | | |
|-----------------------------|---------------------------|-----------------------------------|---------------------------|--|--|--|
| | FLUARIX | TIV-1 | TIV-2 | | | |
| | QUADRIVALENT ^a | (B Victoria) ^b | (B Yamagata) ^c | | | |
| Geometric Mean | n = 1,809 | n = 608 | n = 534 | | | |
| Antibody Titer | (95% CI) | (95% CI) | (95% CI) | | | |
| A/California/7/2009 | 201.1 | 218.4 | 213.0 | | | |
| (H1N1) | (188.1, 215.1) | (194.2, 245.6) | (187.6, 241.9) | | | |
| A/Victoria/210/2009 | 314.7 | 298.2 | 340.4 | | | |
| (H3N2) | (296.8, 333.6) | (268.4, 331.3) | (304.3, 380.9) | | | |
| B/Brisbane/60/2008 | 404.6 | 393.8 | 258.5 | | | |
| (Victoria lineage) | (386.6, 423.4) | (362.7, 427.6) | (234.6, 284.8) | | | |
| B/Brisbane/3/2007 | 601.8 | 386.6 | 582.5 | | | |
| (Yamagata lineage) | (573.3, 631.6) | (351.5, 425.3) | (534.6, 634.7) | | | |
| | n = 1,801 | n = 605 | n = 530 | | | |
| | % | % | % | | | |
| Seroconversion ^d | (95% CI) | (95% CI) | (95% CI) | | | |
| A/California/7/2009 | 77.5 | 77.2 | 80.2 | | | |
| (H1N1) | (75.5, 79.4) | (73.6, 80.5) | (76.5, 83.5) | | | |
| A/Victoria/210/2009 | 71.5 | 65.8 | 70.0 | | | |
| (H3N2) | (69.3, 73.5) | (61.9, 69.6) | (65.9, 73.9) | | | |
| B/Brisbane/60/2008 | 58.1 | 55.4 | 47.5 | | | |
| (Victoria lineage) | (55.8, 60.4) | (51.3, 59.4) | (43.2, 51.9) | | | |
| B/Brisbane/3/2007 | 61.7 | 45.6 | 59.1 | | | |
| (Yamagata lineage) | (59.5, 64.0) | (41.6, 49.7) | (54.7, 63.3) | | | |

ATP = According-to-protocol; CI = Confidence Interval.

ATP cohort for immunogenicity included subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

^a Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

^b Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

^c Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza type B virus of Yamagata lineage.

d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

14.3 Immunological Evaluation of FLUARIX QUADRIVALENT in Children

Trial 7 was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the efficacy of FLUARIX QUADRIVALENT. In this trial, subjects aged 6 through 35 months received FLUARIX QUADRIVALENT (n = 6,006) or a non-influenza control vaccine (n = 6,012). Immune responses to each of the vaccine antigens were evaluated in sera 28 days following 1 or 2 doses in a subgroup of subjects (n = 753 for FLUARIX QUADRIVALENT, n = 579 for control in the ATP cohort for immunogenicity).

Immunogenicity endpoints (GMTs and the percentage of subjects who achieved seroconversion) were analyzed based on the ATP cohort for whom immunogenicity assay results were available after vaccination. Antibody responses for all 4 influenza strains are presented in Table 11.

Table 11. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 28 Days after Last

Vaccination in Children Aged 6 through 35 Months^a (ATP Cohort for Immunogenicity)

| | FLUARIX QUADRIVALENT | Non-Influenza Active Comparator ^{b,c} |
|-----------------------------|-------------------------|---|
| Geometric Mean Antibody | n = 750-753 | n = 578-579 |
| Titer | (95% CI) | (95% CI) |
| A (H1N1) | 165.3 | 12.6 |
| | (148.6, 183.8) | (11.1, 14.3) |
| A (H3N2) | 132.1 | 14.7 |
| | (119.1, 146.5) | (12.9, 16.7) |
| B (Victoria lineage) | 92.6 | 9.2 |
| | (82.3, 104.1) | (8.4, 10.1) |
| B (Yamagata lineage) | 121.4 | 7.6 |
| | (110.1, 133.8) | (7.0, 8.3) |
| | n = 742-746 | n = 566-568 |
| | % | % |
| Seroconversion ^d | (95% CI) | (95% CI) |
| A (H1N1) | 80.2 | 3.5 |
| | (77.2, 83.0) | (2.2, 5.4) |
| A (H3N2) | 68.8 | 4.2 |
| | (65.3, 72.1) | (2.7, 6.2) |
| B (Victoria lineage) | 69.3 | 0.9 |
| | (65.8, 72.6) | (0.3, 2.0) |
| B (Yamagata lineage) | 81.2 | 2.3 |
| | (78.2, 84.0) | (1.2, 3.9) |

ATP = According-to-protocol; CI = Confidence Interval.

ATP cohort for immunogenicity included subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

Trial 2 was a randomized, double-blind, active-controlled, safety, immunogenicity, and non-inferiority trial. In this trial, subjects received FLUARIX QUADRIVALENT (n = 791) or one of 2 formulations of

a Trial 7: NCT01439360.

^b Children younger than 12 months: pneumococcal 13-valent conjugate vaccine [Diphtheria CRM197 Protein] (Wyeth Pharmaceuticals, Inc.).

^c Children 12 months and older: HAVRIX (Hepatitis A Vaccine) for those with a history of influenza vaccination; or HAVRIX (Dose 1) and a varicella vaccine (U.S. Licensed Manufactured by Merck & Co., Inc. or Non-U.S. Licensed Manufactured by GlaxoSmithKline Biologicals) (Dose 2) for those with no history of influenza vaccination.

d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

comparator trivalent influenza vaccine (FLUARIX; TIV-1, n = 819; or TIV-2, n = 801), each containing an influenza type B virus that corresponded to one of the 2 type B viruses in FLUARIX QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). In children aged 3 through 17 years, immune responses to each of the vaccine antigens were evaluated in sera 28 days following 1 or 2 doses. In the overall population, 52% of subjects were male; 56% were white, 29% were Asian, 12% were black, and 3% were of other racial/ethnic groups.

The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the ATP cohort for whom immunogenicity assay results were available after vaccination. FLUARIX QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (upper limit of the 2-sided 95% CI for the GMT ratio [TIV/FLUARIX QUADRIVALENT] ≤1.5) and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLUARIX QUADRIVALENT ≤10%). The antibody response to influenza B strains contained in FLUARIX QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 12).

Table 12. FLUARIX QUADRIVALENT: Immune Responses to Each Antigen 28 Days after Last

Vaccination in Children Aged 3 through 17 Years (ATP Cohort for Immunogenicity)

| | | Trivalent Influenza Vaccine (TIV) | |
|-----------------------------|---------------------------|-----------------------------------|---------------------------|
| | FLUARIX | | |
| | | TIV-1 | TIV-2 |
| | QUADRIVALENT ^a | (B Victoria) ^b | (B Yamagata) ^c |
| Geometric Mean | n = 791 | n = 818 | n = 801 |
| Antibody Titer | (95% CI) | (95% CI) | (95% CI) |
| A/California/7/2009 | 386.2 | 433.2 | 422.3 |
| (H1N1) | (357.3, 417.4) | (401.0, 468.0) | (390.5, 456.5) |
| A/Victoria/210/2009 | 228.8 | 227.3 | 234.0 |
| (H3N2) | (215.0, 243.4) | (213.3, 242.3) | (219.1, 249.9) |
| B/Brisbane/60/2008 | 244.2 | 245.6 | 88.4 |
| (Victoria lineage) | (227.5, 262.1) | (229.2, 263.2) | (81.5, 95.8) |
| B/Brisbane/3/2007 | 569.6 | 224.7 | 643.3 |
| (Yamagata lineage) | (533.6, 608.1) | (207.9, 242.9) | (603.2, 686.1) |
| | n = 790 | n = 818 | n = 800 |
| | % | % | % |
| Seroconversion ^d | (95% CI) | (95% CI) | (95% CI) |
| A/California/7/2009 | 91.4 | 89.9 | 91.6 |
| (H1N1) | (89.2, 93.3) | (87.6, 91.8) | (89.5, 93.5) |
| A/Victoria/210/2009 | 72.3 | 70.7 | 71.9 |
| (H3N2) | (69.0, 75.4) | (67.4, 73.8) | (68.6, 75.0) |
| B/Brisbane/60/2008 | 70.0 | 68.5 | 29.6 |
| (Victoria lineage) | (66.7, 73.2) | (65.2, 71.6) | (26.5, 32.9) |
| B/Brisbane/3/2007 | 72.5 | 37.0 | 70.8 |
| (Yamagata lineage) | (69.3, 75.6) | (33.7, 40.5) | (67.5, 73.9) |

ATP = According-to-protocol; CI = Confidence Interval.

ATP cohort for immunogenicity included subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

^a Contained the same composition as FLUARIX (trivalent formulation) manufactured for the 2010-2011 season and an additional influenza type B virus of Yamagata lineage.

^b Contained the same composition as FLUARIX manufactured for the 2010-2011 season (2 influenza A subtype viruses and an influenza type B virus of Victoria lineage).

^c Contained the same 2 influenza A subtype viruses as FLUARIX manufactured for the 2010-2011 season and an influenza B virus of Yamagata lineage.

d Seroconversion defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum titers of HI antibodies to ≥1:40.

14.4 FLUARIX QUADRIVALENT Concomitant Administration with Zoster Vaccine Recombinant, Adjuvanted (SHINGRIX)

In an open-label, randomized clinical trial (NCT 01954251) in adults aged 50 years and older, there was no evidence for interference in antibody responses (HI antibodies and anti-gE antibodies) to FLUARIX QUADRIVALENT or the coadministered vaccine, SHINGRIX [see Adverse Reactions (6.1)].

15 REFERENCES

- 1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res.* 2004;103:133-138.
- 2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb*. 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 58160-896-41 Syringe in Package of 10: NDC 58160-896-52

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light.

17 PATIENT COUNSELING INFORMATION

Provide the following information to the vaccine recipient or guardian:

- Inform of the potential benefits and risks of immunization with FLUARIX QUADRIVALENT.
- Educate regarding potential side effects, emphasizing that: (1) FLUARIX QUADRIVALENT
 contains non-infectious killed viruses and cannot cause influenza and (2) FLUARIX
 QUADRIVALENT is intended to provide protection against illness due to influenza viruses only and
 cannot provide protection against all respiratory illness.
- Encourage women exposed to FLUARIX QUADRIVALENT during pregnancy to enroll in the pregnancy registry [see Use in Specific Populations (8.1)].
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 prior to each immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Instruct that annual revaccination is recommended.

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EXHIBIT 253

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These highlights do not include all the information needed to use FLULAVAL QUADRIVALENT safely and effectively. See full prescribing information for FLULAVAL QUADRIVALENT.

FLULAVAL QUADRIVALENT (Influenza Vaccine) injectable suspension, for intramuscular use 2019-2020 Formula

Initial U.S. Approval: 2013

-- INDICATIONS AND USAGE-

FLULAVAL QUADRIVALENT is a vaccine indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL QUADRIVALENT is approved for use in persons aged 6 months and older. (1)

------DOSAGE AND ADMINISTRATION-------For intramuscular injection only. (2)

| Age | Vaccination Status | Dose and Schedule |
|-------------|---------------------------|-----------------------------|
| 6 months | Not previously vaccinated | Two doses (0.5-mL each) |
| through | with influenza vaccine | at least 4 weeks apart |
| 8 years | | (2.1) |
| | Vaccinated with influenza | One or 2 doses ^a |
| | vaccine in a previous | (0.5-mL each) (2.1) |
| | season | |
| 9 years and | Not applicable | One 0.5-mL dose (2.1) |
| older | | |

^a One dose or 2 doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of influenza with vaccines. If 2 doses, administer each 0.5-mL dose at least 4 weeks apart. (2.1)

---- DOSAGE FORMS AND STRENGTHS-

Suspension for injection:

- 0.5-mL single-dose prefilled syringes (3)
- 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL). (3)

-----CONTRAINDICATIONS -

History of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine. (4, 11)

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL QUADRIVALENT should be based on careful consideration of the potential benefits and risks. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL QUADRIVALENT.
 Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

---ADVERSE REACTIONS--

- In adults, the most common (≥10%) solicited local adverse reaction was pain (60%); most common solicited systemic adverse reactions were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%). (6.1)
- In children aged 6 through 35 months, the most common (≥10%) solicited local adverse reaction was pain (40%); most common solicited systemic adverse reactions were irritability (49%), drowsiness (37%), and loss of appetite (29%). (6.1)
- In children aged 3 through 17 years, the most common (≥10%) solicited local adverse reaction was pain (65%). (6.1)
- In children aged 3 through 4 years, the most common (≥10%) solicited systemic adverse reactions were irritability (26%), drowsiness (21%), and loss of appetite (17%). (6.1)
- In children aged 5 through 17 years, the most common (≥10%) solicited systemic adverse reactions were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

---- USE IN SPECIFIC POPULATIONS---

Geriatric Use: Antibody responses were lower in geriatric subjects who received FLULAVAL QUADRIVALENT than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/20xx

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLULAVAL QUADRIVALENT is indicated for active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. FLULAVAL QUADRIVALENT is approved for use in persons aged 6 months and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular injection only.

2.1 Dosage and Schedule

The dose and schedule for FLULAVAL QUADRIVALENT are presented in Table 1.

Table 1. FLULAVAL QUADRIVALENT: Dosing

| 8 | | | | |
|--------------------------|------------------------------|-------------------------------------|--|--|
| Age | Vaccination Status | Dose and Schedule | | |
| 6 months through 8 years | Not previously vaccinated | Two doses (0.5-mL each) | | |
| | with influenza vaccine | at least 4 weeks apart | | |
| | Vaccinated with influenza | One or 2 doses ^a (0.5-mL | | |
| | vaccine in a previous season | each) | | |
| 9 years and older | Not applicable | One 0.5-mL dose | | |

^a One dose or 2 doses (0.5-mL each) depending on vaccination history as per the annual Advisory Committee on Immunization Practices (ACIP) recommendation on prevention and control of seasonal influenza with vaccines. If 2 doses, administer each 0.5-mL dose at least 4 weeks apart.

2.2 Administration Instructions

Shake well before administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Attach a sterile needle to the prefilled syringe and administer intramuscularly.

For the multi-dose vial, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose from the multi-dose vial and administer intramuscularly. A sterile syringe with a needle bore no larger than 23 gauge is recommended for administration. It is recommended that small syringes (0.5 mL or 1 mL) be used to minimize any product loss. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial.

Between uses, return the multi-dose vial to the recommended storage conditions, between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Once entered, a multi-dose vial, and any residual contents should be discarded after 28 days.

The preferred sites for intramuscular injection are the anterolateral thigh for children aged 6 through

11 months and the deltoid muscle of the upper arm for persons aged 12 months and older. Do not inject in the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously, intradermally, or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLULAVAL QUADRIVALENT is a suspension for injection available in 0.5-mL prefilled TIP-LOK syringes and 5-mL multi-dose vials containing 10 doses (each dose is 0.5 mL).

4 CONTRAINDICATIONS

Do not administer FLULAVAL QUADRIVALENT to anyone with a history of severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or following a previous dose of any influenza vaccine [see Description (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give FLULAVAL QUADRIVALENT should be based on careful consideration of the potential benefits and risks.

The 1976 swine influenza vaccine was associated with an elevated risk of GBS. Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case/1 million persons vaccinated.

5.2 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including FLULAVAL QUADRIVALENT. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.3 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of FLULAVAL QUADRIVALENT.

5.4 Altered Immunocompetence

If FLULAVAL QUADRIVALENT is administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the immune response may be lower than in immunocompetent persons.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL QUADRIVALENT may not protect all susceptible individuals.

5.6 Persons at Risk of Bleeding

As with other intramuscular injections, FLULAVAL QUADRIVALENT should be given with caution in individuals with bleeding disorders such as hemophilia or on anticoagulant therapy to avoid the risk of hematoma following the injection.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of FLULAVAL QUADRIVALENT could reveal adverse reactions not observed in clinical trials.

In adults who received FLULAVAL QUADRIVALENT, the most common (\geq 10%) solicited local adverse reaction was pain (60%); the most common (\geq 10%) solicited systemic adverse reactions were muscle aches (26%), headache (22%), fatigue (22%), and arthralgia (15%).

In children aged 6 through 35 months who received FLULAVAL QUADRIVALENT, the most common (\geq 10%) solicited local adverse reaction was pain (40%); the most common (\geq 10%) solicited systemic adverse reactions were irritability (49%), drowsiness (37%), and loss of appetite (29%).

In children aged 3 through 17 years who received FLULAVAL QUADRIVALENT, the most common (\geq 10%) solicited local adverse reaction was pain (65%). In children aged 3 through 4 years, the most common (\geq 10%) solicited systemic adverse reactions were irritability (26%), drowsiness (21%), and loss of appetite (17%). In children aged 5 through 17 years, the most common (\geq 10%) systemic adverse reactions were muscle aches (29%), fatigue (22%), headache (22%), arthralgia (13%), and gastrointestinal symptoms (10%).

FLULAVAL QUADRIVALENT has been administered in 8 clinical trials to 1,384 adults aged 18 years and older, 1,965 children aged 6 through 35 months, and 3,516 children aged 3 through 17 years.

FLULAVAL QUADRIVALENT in Adults

Trial 1 (NCT01196975) was a randomized, double-blind, active-controlled, safety and immunogenicity trial. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 1,272), or one of 2 formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, n = 213 or TIV-2, n = 218), each containing an influenza type B virus that corresponded to one of the 2 B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 18 years and older (mean age: 50 years) and 61% were female; 61% of subjects were white, 3% were black, 1% were Asian, and 35% were of other

racial/ethnic groups. Solicited adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of solicited adverse reactions occurring within 7 days of vaccination in adults are shown in Table 2.

Table 2. FLULAVAL QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a of Vaccination in Adults Aged 18 Years and Older^b (Total Vaccinated

Cohort)

| , | | | Trivale | nt Influen | za Vaccin | e (TIV) |
|--|----------|----------------------|---------|---------------------|---------------------------|----------|
| | FLULAVAL | | TIV-1 | | TIV-2 | |
| | QUADRI | VALENT ^c | (B Vic | toria) ^d | (B Yamagata) ^e | |
| | n = 1 | ,260 | n = | 208 | n = 216 | |
| | 9/ | 0 | 0 | ⁄o | 0 | ⁄o |
| Adverse Reaction | Any | Grade 3 ^f | Any | Grade 3f | Any | Grade 3f |
| Local | | | | | | |
| Pain | 60 | 2 | 45 | 1 | 41 | 1 |
| Swelling | 3 | 0 | 1 | 0 | 4 | 0 |
| Redness | 2 | 0 | 3 | 0 | 1 | 0 |
| Systemic | | | | | | • |
| Muscle aches | 26 | 1 | 25 | 1 | 19 | 1 |
| Headache | 22 | 1 | 20 | 1 | 23 | 0 |
| Fatigue | 22 | 1 | 22 | 1 | 17 | 2 |
| Arthralgia | 15 | 1 | 17 | 1 | 15 | 3 |
| Gastrointestinal symptoms ^g | 9 | 1 | 10 | 2 | 7 | 1 |
| Shivering | 9 | 1 | 8 | 1 | 6 | 1 |
| Fever ^h | 1 | 0 | 1 | 0 | 1 | 1 |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. n = Number of subjects with diary card completed.

Grade 3 swelling, redness: Defined as >100 mm.

Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.

Grade 3 (or higher) fever: Defined as $\geq 102.2^{\circ}F$ (39.0°C).

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 1: NCT01196975.

^c Contained 2 A strains and 2 B strains, one of Victoria lineage and one of Yamagata lineage.

^d Contained the same 2 A strains as FLULAVAL QUADRIVALENT and a B strain of Victoria lineage.

^e Contained the same 2 A strains as FLULAVAL QUADRIVALENT and a B strain of Yamagata lineage.

f Grade 3 pain: Defined as significant pain at rest; prevented normal everyday activities.

g Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

h Fever: Defined as ≥100.4°F (38.0°C)

Unsolicited adverse events occurring within 21 days of vaccination were reported in 19%, 23%, and 23% of subjects who received FLULAVAL QUADRIVALENT (n = 1,272), TIV-1 (B Victoria) (n = 213), or TIV-2 (B Yamagata) (n = 218), respectively. The unsolicited adverse reactions that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included nasopharyngitis, upper respiratory tract infection, headache, cough, and oropharyngeal pain. Serious adverse events occurring within 21 days of vaccination were reported in 0.4%, 0%, and 0% of subjects who received FLULAVAL QUADRIVALENT, TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

FLULAVAL QUADRIVALENT in Children

Trial 4 (NCT02242643) was a randomized, observer-blind, active-controlled immunogenicity and safety trial. The trial included subjects aged 6 through 35 months who received FLULAVAL QUADRIVALENT (n = 1,207) or FLUZONE QUADRIVALENT, a U.S.-licensed inactivated influenza vaccine (n = 1,217) used as comparator, manufactured by Sanofi Pasteur Inc. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or the comparator vaccine approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or the comparator vaccine. In the overall population, 53% were male; 64% were white, 16% were black, 3% were Asian, and 17% were of other racial/ethnic groups. The mean age of subjects was 20 months. Subjects were followed for safety for 6 months; solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days) post vaccination. The incidence of solicited adverse reactions occurring within 7 days of vaccination in children are shown in Table 3.

Table 3. FLULAVAL QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a of First Vaccination in Children Aged 6 through 35 Months^b (Total

Vaccinated Cohort)

| | FLULAVAL QUADRIVALENT % | | | mparator ^c |
|--------------------|-------------------------------|---|-----------|-----------------------|
| Adverse Reaction | Any Grade 3 ^d | | Any | Grade 3 ^d |
| Local | n = 1,151 | | n = 1,146 | |
| Pain | 40 | 2 | 37 | 1 |
| Swelling | 1 | 0 | 0 | 0 |
| Redness | 1 | 0 | 1 | 0 |
| Systemic | n = 1,155 | | n = 1,148 | |
| Irritability | 49 | 4 | 46 | 3 |
| Drowsiness | 37 | 3 | 37 | 3 |
| Loss of appetite | 29 | 2 | 29 | 1 |
| Fever ^e | 6 | 1 | 6 | 1 |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available (i.e., diary card completed for solicited symptoms).

Grade 3 swelling, redness: Defined as >100 mm.

Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.

Grade 3 drowsiness: Defined as prevented normal activity.

Grade 3 loss of appetite: Defined as not eating at all.

Grade 3 (or higher) fever: Defined as >102.2°F (39.0°C).

In children who received a second dose of FLULAVAL QUADRIVALENT or the comparator vaccine, the incidences of solicited adverse reactions following the second dose were generally similar or lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 46% and 44% of subjects who received FLULAVAL QUADRIVALENT (n = 1,207) and the comparator vaccine (n = 1,217), respectively. The unsolicited adverse reactions that occurred most frequently (≥1%) for FLULAVAL QUADRIVALENT included upper respiratory tract infection, cough, diarrhea, pyrexia, vomiting, and rash. Serious adverse events occurring during the study period (approximately 6 months) were reported in 2% of subjects who received FLULAVAL QUADRIVALENT and in 2% of subjects who received the comparator vaccine. There were no deaths reported during the study period.

n = Number of subjects with diary card completed.

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 4: NCT02242643.

^c U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc).

d Grade 3 pain: Defined as cried when limb was moved/spontaneously painful.

e Fever: Defined as \geq 100.4°F (38.0°C).

Trial 2 (NCT01198756) was a randomized, double-blind, active-controlled trial. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 932) or one of 2 formulations of a comparator trivalent influenza vaccine [FLUARIX (Influenza Vaccine), TIV-1 (B Victoria), n = 929 or TIV-2 (B Yamagata), n = 932], each containing an influenza type B virus that corresponded to one of the 2 B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The population was aged 3 through 17 years (mean age: 9 years) and 53% were male; 65% were white, 13% were Asian, 9% were black, and 13% were of other racial/ethnic groups. Children aged 3 through 8 years with no history of influenza vaccination received 2 doses approximately 28 days apart. Children aged 3 through 8 years with a history of influenza vaccination and children aged 9 years and older received one dose. Solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of solicited adverse reactions occurring within 7 days of vaccination in children are shown in Table 4.

Table 4. FLULAVAL QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a of First Vaccination in Children Aged 3 through 17 Years^b (Total

Vaccinated Cohort)

| vaccinated Conort) | | | | | | |
|----------------------------|-------|----------------------|----------------------|-----------------------|------------|----------------------|
| | | | Trival | ent Influen | za Vaccine | (TIV) |
| | FLUI | LAVAL | TIV-1 | | TIV-2 | |
| | QUADR | IVALENT ^c | (B Vic | toria) ^d | (B Yan | nagata) ^e |
| | _ | % | - | ⁄o ´ | ` | 6 |
| | Any | Grade 3 ^f | Any | Grade 3 ^f | Any | Grade 3 ^f |
| Adverse Reaction | * | | | ugh 17 Year | | |
| Local | n = | = 913 | n = | 911 | n = | 915 |
| Pain | 65 | 3 | 55 | 2 | 56 | 2 |
| Swelling | 6 | 0 | 3 | 0 | 4 | 0 |
| Redness | 5 | 0 | 3 | 0 | 4 | 0 |
| | | A | ged 3 thro | ged 3 through 4 Years | | |
| Systemic | n = | = 185 | n = | 187 | n = | 189 |
| Irritability | 26 | 1 | 17 | 0 | 22 | 2 |
| Drowsiness | 21 | 0 | 20 | 2 | 23 | 1 |
| Loss of appetite | 17 | 0 | 16 | 2 | 13 | 1 |
| Fever ^g | 5 | 1 | 6 | 1 | 4 | 2 |
| | | A | ged 5 through 17 Yea | | rs | |
| Systemic | n = | = 727 | n = 724 | | n = 725 | |
| Muscle aches | 29 | 1 | 25 | 1 | 25 | 1 |
| Fatigue | 22 | 1 | 24 | 2 | 23 | 1 |
| Headache | 22 | 1 | 22 | 1 | 20 | 1 |
| Arthralgia | 13 | 0 | 12 | 1 | 11 | 0 |
| Gastrointestinal symptomsh | 10 | 1 | 10 | 1 | 9 | 1 |
| Shivering | 7 | 0 | 7 | 1 | 7 | 1 |
| Fever ^g | 2 | 1 | 4 | 1 | 3 | 0 |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. N = number of subjects with diary card completed.

Grade 3 swelling, redness: Defined as >100 mm.

Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.

Grade 3 drowsiness: Defined as prevented normal activity.

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 2: NCT01198756.

^c Contained 2 A strains and 2 B strains, one of Victoria lineage and one of Yamagata lineage.

d Contained the same 2 A strains as FLULAVAL QUADRIVALENT and a B strain of Victoria lineage.

^e Contained the same 2 A strains as FLULAVAL QUADRIVALENT and a B strain of Yamagata lineage.

f Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <5 years), or significant pain at rest, prevented normal everyday activities (children ≥5 years).

Grade 3 loss of appetite: Defined as not eating at all.

Grade 3 (or higher) fever: Defined as ≥ 102.2 °F (39.0°C).

Grade 3 muscle aches, fatigue, headache, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.

- g Fever: Defined as ≥ 100.4 °F (38.0°C).
- h Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

In children who received a second dose of FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata), the incidences of adverse reactions following the second dose were generally lower than those observed after the first dose.

Unsolicited adverse events occurring within 28 days of vaccination were reported in 30%, 31%, and 30% of subjects who received FLULAVAL QUADRIVALENT (n = 932), FLUARIX TIV-1 (B Victoria) (n = 929), or TIV-2 (B Yamagata) (n = 932), respectively. The unsolicited adverse reactions that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included vomiting, pyrexia, bronchitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, and rhinorrhea. Serious adverse events occurring within 28 days of any vaccination were reported in 0.1%, 0.2%, and 0.2% of subjects who received FLULAVAL QUADRIVALENT, FLUARIX TIV-1 (B Victoria), or TIV-2 (B Yamagata), respectively.

Trial 3 (NCT01218308) was a randomized, observer-blind, non-influenza vaccine-controlled trial evaluating the efficacy of FLULAVAL QUADRIVALENT. The trial included subjects aged 3 through 8 years who received FLULAVAL QUADRIVALENT (n = 2,584) or HAVRIX (Hepatitis A Vaccine) (n = 2,584) as a control vaccine. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart (this dosing regimen for HAVRIX is not a U.S.-licensed schedule). Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or HAVRIX. In the overall population, 52% were male; 60% were Asian, 5% were white, and 35% were of other racial/ethnic groups. The mean age of subjects was 5 years. Solicited local adverse reactions and systemic adverse events were collected for 7 days (day of vaccination and the next 6 days). The incidence of solicited adverse reactions occurring within 7 days of vaccination in children are shown in Table 5.

Table 5. FLULAVAL QUADRIVALENT: Incidence of Solicited Local and Systemic Adverse Reactions within 7 Days^a of First Vaccination in Children Aged 3 through 8 Years^b (Total

Vaccinated Cohort)

| vaccinated Conort) | | | | |
|--|--------------------------|----------------------|---------------------|----------------------|
| | FLULAVAL QUADRIVALENT | | HAVRIX ^c | |
| | | % | 0 | ⁄ o |
| | Any | Grade 3 ^d | Any | Grade 3 ^d |
| Adverse Reaction | | Aged 3 thro | ugh 8 Years | |
| Local | n = | 2,546 | $\mathbf{n} = 2$ | 2,551 |
| Pain | 39 | 1 | 28 | 1 |
| Swelling | 1 | 0 | 0 | 0 |
| Redness | 0 | 0 | 0 | 0 |
| | | Aged 3 thro | ugh 4 Years | |
| Systemic | n = | = 898 | n = 895 | |
| Loss of appetite | 9 | 0 | 8 | 0 |
| Irritability | 8 | 0 | 8 | 0 |
| Drowsiness | 8 | 0 | 7 | 0 |
| Fever ^e | 4 | 1 | 4 | 1 |
| | | Aged 5 thro | ugh 8 Years | |
| Systemic | n = | 1,648 | $\mathbf{n} = 1$ | 1,654 |
| Muscle aches | 12 | 0 | 10 | 0 |
| Headache | 11 | 0 | 11 | 1 |
| Fatigue | 8 | 0 | 7 | 0 |
| Arthralgia | 6 | 0 | 5 | 0 |
| Gastrointestinal symptoms ^f | 6 | 0 | 6 | 0 |
| Shivering | 3 | 0 | 3 | 0 |
| Fever ^e | 3 | 1 | 3 | 1 |

Total vaccinated cohort for safety included all vaccinated subjects for whom safety data were available. N = number of subjects with diary card completed.

Grade 3 swelling, redness: Defined as >100 mm.

Grade 3 loss of appetite: Defined as not eating at all.

Grade 3 irritability: Defined as crying that could not be comforted/prevented normal activity.

Grade 3 drowsiness: Defined as prevented normal activity.

Grade 3 (or higher) fever: Defined as $\geq 102.2^{\circ}F$ (39.0°C).

^a Seven days included day of vaccination and the subsequent 6 days.

^b Trial 3: NCT01218308.

^c Hepatitis A Vaccine used as a control vaccine.

d Grade 3 pain: Defined as cried when limb was moved/spontaneously painful (children <5 years), or significant pain at rest, prevented normal everyday activities (children ≥5 years).

Grade 3 muscle aches, headache, fatigue, arthralgia, gastrointestinal symptoms, shivering: Defined as prevented normal activity.

In children who received a second dose of FLULAVAL QUADRIVALENT or HAVRIX, the incidences of adverse reactions following the second dose were generally lower than those observed after the first dose.

The frequency of unsolicited adverse events occurring within 28 days of vaccination was similar in both groups (33% for both FLULAVAL QUADRIVALENT and HAVRIX). The unsolicited adverse reactions that occurred most frequently (≥1% for FLULAVAL QUADRIVALENT) included diarrhea, pyrexia, gastroenteritis, nasopharyngitis, upper respiratory tract infection, varicella, cough, and rhinorrhea. Serious adverse events occurring within 28 days of any vaccination were reported in 0.7% of subjects who received FLULAVAL QUADRIVALENT and in 0.2% of subjects who received HAVRIX.

6.2 Postmarketing Experience

Beyond those events reported in the clinical trials for FLULAVAL QUADRIVALENT or FLULAVAL, the following adverse reactions have been identified during postapproval use of FLULAVAL QUADRIVALENT or FLULAVAL (trivalent influenza vaccine). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

Blood and Lymphatic System Disorders

Lymphadenopathy.

Eye Disorders

Eye pain, photophobia.

Gastrointestinal Disorders

Dysphagia, vomiting.

General Disorders and Administration Site Conditions

Chest pain, injection site inflammation, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess.

Immune System Disorders

Allergic reactions including anaphylaxis, angioedema.

Infections and Infestations

Rhinitis, laryngitis, cellulitis.

e Fever: Defined as \geq 100.4°F (38.0°C).

f Gastrointestinal symptoms included nausea, vomiting, diarrhea, and/or abdominal pain.

Musculoskeletal and Connective Tissue Disorders

Muscle weakness, arthritis.

Nervous System Disorders

Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guilla in-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

Psychiatric Disorders

Insomnia.

Respiratory, Thoracic, and Mediastinal Disorders

Dyspnea, dysphonia, bronchospasm, throat tightness.

Skin and Subcutaneous Tissue Disorders

Urticaria, localized or generalized rash, pruritus, sweating.

Vascular Disorders

Flushing, pallor.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

FLULAVAL QUADRIVALENT should not be mixed with any other vaccine in the same syringe or vial.

There are insufficient data to assess the concomitant administration of FLULAVAL QUADRIVALENT with other vaccines. When concomitant administration of other vaccines is required, the vaccines should be administered at different injection sites.

7.2 Immunos uppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses) may reduce the immune response to FLULAVAL QUADRIVALENT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FLULAVAL QUADRIVALENT during pregnancy. Healthcare providers are encouraged to register women by calling 1-888-452-9622.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There are insufficient data on FLULAVAL QUADRIVALENT in pregnant women to inform vaccine-associated risks.

A developmental toxicity study was performed in female rats administered FLULAVAL QUADRIVALENT prior to mating and during gestation and lactation periods. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). This study revealed no adverse effects on fetal or pre-weaning development due to FLULAVAL QUADRIVALENT (see Data).

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women infected with seasonal influenza are at increased risk of severe illness associated with influenza infection compared with non-pregnant women. Pregnant women with influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

Data

Animal Data: In a developmental toxicity study, female rats were administered FLULAVAL QUADRIVALENT by intramuscular injection 4 and 2 weeks prior to mating, on Gestation Days 3, 8, 11, and 15, and on Lactation Day 7. The total dose was 0.2 mL at each occasion (a single human dose is 0.5 mL). No adverse effects on pre-weaning development up to Postnatal Day 25 were observed. There were no vaccine-related fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether FLULAVAL QUADRIVALENT is excreted in human milk. Data are not available to assess the effects of FLULAVAL QUADRIVALENT on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLULAVAL QUADRIVALENT and any potential adverse effects on the breastfed child from FLULAVAL QUADRIVALENT or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of FLULAVAL QUADRIVALENT in children younger than 6 months have not been established.

8.5 Geriatric Use

In a randomized, double-blind, active-controlled trial, immunogenicity and safety were evaluated in a

cohort of subjects aged 65 years and older who received FLULAVAL QUADRIVALENT (n = 397); approximately one-third of these subjects were aged 75 years and older. In subjects aged 65 years and older, the geometric mean antibody titers (GMTs) post-vaccination and seroconversion rates were lower than in younger subjects (aged 18 to 64 years) and the frequencies of solicited and unsolicited adverse reactions were generally lower than in younger subjects [see Adverse Reactions (6.1), Clinical Studies (14.2)].

11 DESCRIPTION

FLULAVAL QUADRIVALENT, Influenza Vaccine, for intramuscular injection, is a quadrivalent, split-virion, inactivated influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza viruses is produced and purified separately. The virus is inactivated with ultraviolet light treatment followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

FLULAVAL QUADRIVALENT is a sterile, opalescent, translucent to off-white suspension in a phosphate-buffered saline solution that may sediment slightly. The sediment resuspends upon shaking to form a homogeneous suspension.

FLULAVAL QUADRIVALENT has been standardized according to U.S. Public Health Service (USPHS) requirements for the 2019-2020 influenza season and is formulated to contain 60 micrograms (mcg) hemagglutinin (HA) per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 4 influenza virus strains (2 A strains and 2 B strains): A/Brisbane/02/2018 (H1N1) pdm09 (IVR-190), A/Kansas/14/2017 (H3N2) X-327, B/Maryland/15/2016 NYMC BX-69A (a B/Colorado/06/2017-like virus), and B/Phuket/3073/2013.

The prefilled syringe is formulated without preservatives and does not contain thimerosal. Each 0.5-mL dose from the multi-dose vial contains 50 mcg thimerosal (<25 mcg mercury); thimerosal, a mercury derivative, is added as a preservative.

Each 0.5-mL dose of either presentation may also contain residual amounts of ovalbumin (\leq 0.3 mcg), formaldehyde (\leq 25 mcg), sodium deoxycholate (\leq 50 mcg), α -tocopheryl hydrogen succinate (\leq 320 mcg), and polysorbate 80 (\leq 887 mcg) from the manufacturing process. Antibiotics are not used in the manufacture of this vaccine.

The tip caps and plungers of the prefilled syringes are not made with natural rubber latex. The vial stoppers are not made with natural rubber latex.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation.

Public health authorities recommend influenza vaccine strains annually. Inactivated influenza vaccines are standardized to contain the hemagglutinins of strains representing the influenza viruses likely to circulate in the United States during the influenza season.

Specific levels of hemagglutination inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies, antibody titers of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects. ^{1,2} Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine.

Annual revaccination is recommended because immunity declines during the year after vaccination and because circulating strains of influenza virus change from year to year.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL QUADRIVALENT has not been evaluated for carcinogenic, mutagenic potential, or male infertility in animals. Vaccination of female rats with FLULAVAL QUADRIVALENT had no effect on fertility [see Use in Specific Populations (8.1)].

14 CLINICAL STUDIES

14.1 Efficacy against Influenza

The efficacy of FLULAVAL QUADRIVALENT was evaluated in Trial 3, a randomized, observerblind, non-influenza vaccine-controlled trial conducted in 3 countries in Asia, 3 in Latin America, and 2 in the Middle East/Europe during the 2010-2011 influenza season. Healthy subjects aged 3 through 8 years were randomized (1:1) to receive FLULAVAL QUADRIVALENT (n = 2,584), containing A/California/7/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/4/2006 (Yamagata lineage) influenza strains, or HAVRIX (n = 2,584), as a control vaccine. Children with no history of influenza vaccination received 2 doses of FLULAVAL QUADRIVALENT or HAVRIX approximately 28 days apart. Children with a history of influenza vaccination received one dose of FLULAVAL QUADRIVALENT or HAVRIX [see Adverse Reactions (6.1)]. In the overall population, 52% were male; 60% were Asian, 5% were white, and 35% were of other racial/ethnic groups. The mean age of subjects was 5 years.

Efficacy of FLULAVAL QUADRIVALENT was assessed for the prevention of reverse transcriptase polymerase chain reaction (RT-PCR)-positive influenza A and/or B disease presenting as influenza-like illness (ILI). ILI was defined as a temperature ≥100°F in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose, or nasal congestion. Subjects with ILI

(monitored by passive and active surveillance for approximately 6 months) had nasal and throat swabs collected and tested for influenza A and/or B by RT-PCR. All RT-PCR-positive specimens were further tested in cell culture. Vaccine efficacy was calculated based on the ATP cohort for efficacy (Table 6).

Table 6. FLULAVAL QUADRIVALENT: Influenza Attack Rates and Vaccine Efficacy against Influenza A and/or B in Children Aged 3 through 8 Years (According-to-Protocol Cohort for

Efficacy)

| | N ^b | n ^c | Influenza Attack Rate % (n/N) | Vaccine Efficacy % (CI) |
|-----------------------------------|----------------|----------------|-------------------------------------|----------------------------|
| All RT-PCR-Positive Influenza | | | | |
| FLULAVAL QUADRIVALENT | 2,379 | 58 | 2.4 | 55.4 ^d |
| | | | | (95% CI: 39.1, 67.3) |
| HAVRIXe | 2,398 | 128 | 5.3 | _ |
| All Culture-Confirmed Influenzaf | | | | |
| FLULAVAL QUADRIVALENT | 2,379 | 50 | 2.1 | 55.9 |
| | | | | (97.5% CI: 35.4, 69.9) |
| HAVRIX ^e | 2,398 | 112 | 4.7 | _ |
| Antigenically Matched Culture-Con | ifirmed Inf | lue nza | | |
| FLULAVAL QUADRIVALENT | 2,379 | 31 | 1.3 | 45.1g |
| | | | | (97.5% CI: 9.3, 66.8) |
| HAVRIXe | 2,398 | 56 | 2.3 | _ |

CI = Confidence Interval; RT-PCR = Reverse transcriptase polymerase chain reaction.

In an exploratory analysis by age, vaccine efficacy against RT-PCR-positive influenza A and/or B disease presenting as ILI was evaluated in subjects aged 3 through 4 years and 5 through 8 years; vaccine efficacy was 35.3% (95% CI: -1.3, 58.6) and 67.7% (95% CI: 49.7, 79.2), respectively. As the

^a Trial 3: NCT01218308.

^b According-to-protocol cohort for efficacy included subjects who met all eligibility criteria, were successfully contacted at least once post-vaccination, and complied with the protocol-specified efficacy criteria.

^c Number of influenza cases.

^d Vaccine efficacy for FLULAVAL QUADRIVALENT met the pre-defined criterion of >30% for the lower limit of the 2-sided 95% CI.

^e Hepatitis A Vaccine used as a control vaccine.

f Of 162 culture-confirmed influenza cases, 108 (67%) were antigenically typed (87 matched; 21 unmatched); 54 (33%) could not be antigenically typed [but were typed by RT-PCR and nucleic acid sequence analysis: 5 cases A (H1N1) (5 with HAVRIX), 47 cases A (H3N2) (10 with FLULAVAL QUADRIVALENT; 37 with HAVRIX), and 2 cases B Victoria (2 with HAVRIX)].

g Since only 67% of cases could be typed, the clinical significance of this result is unknown.

trial lacked statistical power to evaluate efficacy within age subgroups, the clinical significance of these results is unknown.

As a secondary objective in the trial, subjects with RT-PCR-positive influenza A and/or B were prospectively classified based on the presence of adverse outcomes that have been associated with influenza infection (defined as fever >102.2°F/39.0°C, physician-verified shortness of breath, pneumonia, wheezing, bronchitis, bronchiolitis, pulmonary congestion, croup, and/or acute otitis media, and/or physician-diagnosed serious extra-pulmonary complications, including myositis, encephalitis, seizure and/or myocarditis).

The risk reduction of fever >102.2°F/39.0°C associated with RT-PCR-positive influenza was 71.0% (95% CI: 44.8, 84.8) based on the ATP cohort for efficacy [FLULAVAL QUADRIVALENT (n = 12/2,379); HAVRIX (n = 41/2,398)]. The other pre-specified adverse outcomes had too few cases to calculate a risk reduction. The incidence of these adverse outcomes is presented in Table 7.

Table 7. FLULAVAL QUADRIVALENT: Incidence of Adverse Outcomes Associated with RT-PCR-Positive Influenza in Children Aged 3 through 8 Years a (Total Vaccinated Cohort)^b

| | FLULAVAL QUADRIVALENT | | | | | |
|-----------------------|--------------------------|------------|-----|-----------------|-----------------------|-----|
| | | n = 2,584 | | | n = 2,584 | |
| | Number | Number of | | Number | Number of | |
| Adverse Outcomed | of Events | Subjects e | % | of Events | Subjects ^e | % |
| Fever >102.2°F/39.0°C | 16 ^f | 15 | 0.6 | 51 ^f | 50 | 1.9 |
| Shortness of breath | 0 | 0 | 0 | 5 | 5 | 0.2 |
| Pneumonia | 0 | 0 | 0 | 3 | 3 | 0.1 |
| Wheezing | 1 | 1 | 0 | 1 | 1 | 0 |
| Bronchitis | 1 | 1 | 0 | 1 | 1 | 0 |
| Pulmonary congestion | 0 | 0 | 0 | 1 | 1 | 0 |
| Acute otitis media | 0 | 0 | 0 | 1 | 1 | 0 |
| Bronchiolitis | 0 | 0 | 0 | 0 | 0 | 0 |
| Croup | 0 | 0 | 0 | 0 | 0 | 0 |
| Encephalitis | 0 | 0 | 0 | 0 | 0 | 0 |
| Myocarditis | 0 | 0 | 0 | 0 | 0 | 0 |
| Myositis | 0 | 0 | 0 | 0 | 0 | 0 |
| Seizure | 0 | 0 | 0 | 0 | 0 | 0 |

a Trial 3: NCT01218308.

14.2 Immunological Evaluation

Adults

Trial 1 was a randomized, double-blind, active-controlled, safety and immunogenicity trial conducted in subjects aged 18 years and older. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 1,246) or one of 2 formulations of a comparator trivalent influenza vaccine (FLULAVAL, TIV-1, n = 204 or TIV-2, n = 211), each containing an influenza type B virus that corresponded to one of the 2 B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage) [see Adverse Reactions (6.1)].

Immune responses, specifically hemagglutination inhibition (HI) antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 21 days after administration of FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoint was GMTs adjusted for

^b Total vaccinated cohort included all vaccinated subjects for whom data were available.

^c Hepatitis A Vaccine used as a control vaccine.

^d In subjects who presented with more than one adverse outcome, each outcome was counted in the respective category.

^e Number of subjects presenting with at least one event in each group.

f One subject in each group had sequential influenza due to influenza type A and type B viruses.

baseline, performed on the According-to-Protocol (ATP) cohort for whom immunogenicity assay results were available after vaccination. FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs (Table 8). The antibody response to influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 8).

Table 8. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) 21 Days Post-vaccination in Adults Aged 18 Years and Older^a (According-to-

Protocol Cohort for Immunogenicity)^b

| | FLULAVAL | TIV-1 | TIV-2 |
|----------------------------|-----------------------------------|---------------------------|---------------------------|
| | QUADRIVALENT ^c | (B Victoria) ^d | (B Yamagata) ^e |
| Geometric Mean Titers | n = 1,245-1,246 | n = 204 | n = 210-211 |
| Against | (95% CI) | (95% CI) | (95% CI) |
| A/California/7/2009 (H1N1) | 204.6 ^f | 176.0 | 149.0 |
| | (190.4, 219.9) | (149.1, 207.7) | (122.9, 180.7) |
| A/Victoria/210/2009 (H3N2) | 125.4 ^f (117.4, 133.9) | 147.5 (124.1, 175.2) | 141.0 (118.1, 168.3) |
| B/Brisbane/60/2008 | 177.7 ^f (167.8, 188.1) | 135.9 | 71.9 |
| (Victoria lineage) | | (118.1, 156.5) | (61.3, 84.2) |
| B/Florida/4/2006 | 399.7 ^f (378.1, 422.6) | 176.9 | 306.6 |
| (Yamagata lineage) | | (153.8, 203.5) | (266.2, 353.3) |

CI = Confidence Interval.

Children

Trial 4 was a randomized, observer-blind, active-controlled trial in children aged 6 through 35 months

^a Trial 1: NCT01196975.

^b According-to-protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

^c Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

^d Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

^e Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage).

f Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (TIV/FLULAVAL QUADRIVALENT)≤1.5]; superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI for the GMT ratio (FLULAVAL QUADRIVALENT/TIV)>1.5].

which was conducted in the United States and Mexico. In this trial, subjects received 0.5 mL of FLULAVAL QUADRIVALENT containing 15 mcg HA of each of the 4 influenza strains included in the vaccine (n = 1,207); or 0.25 mL of control vaccine FLUZONE QUADRIVALENT (Influenza Vaccine) containing 7.5 mcg HA of each of the 4 influenza strains included in the vaccine (n = 1,217) [see Adverse Reactions (6.1)].

Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 28 days following completion of vaccination regimen. Previously vaccinated children received one dose and previously unvaccinated children (i.e., unprimed individuals) received 2 doses 4 weeks apart of FLULAVAL QUADRIVALENT or the comparator. The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as a pre-vaccination HI titer of <1:10 with a post-vaccination titer ≥1:40 or at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the ATP cohort. FLULAVAL QUADRIVALENT was non-inferior to the comparator for all 4 vaccine strains based on adjusted GMTs and seroconversion rates (Table 9).

Table 9. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Comparator Quadrivalent Influenza Vaccine at 28 Days Post-vaccination in Children Aged 6 through 35

Months^a (According-to-Protocol Cohort for Immunogenicity)^b

| | FLULAVAL | |
|---|---------------------------|--------------------------------|
| Adjusted Geometric Mean | QUADRIVALENT ^c | Active Comparator ^d |
| Titers Against | n = 972-974 | n = 980 |
| A/California/07/2009 (H1N1) | 99.6° | 85.1 |
| A/Texas/50/2012 (H3N2) | 99.8 ^e | 84.6 |
| B/Massachusetts/02/2012 (Yamagata lineage) | 258.1° | 167.3 |
| B/Brisbane/60/2008 (Victoria lineage) | 54.5° | 33.7 |
| | n = 972-974 | n = 980 |
| | 0 / ₀ | % |
| Seroconversion ^f to: | (95% CI) | (95% CI) |
| A/California/07/2009 (H1N1) | 73.7e | 67.3 |
| | (70.8, 76.4) | (64.3, 70.3) |
| A/Texas/50/2012 | 76.1 ^e | 69.4 |
| (H3N2) | (73.3, 78.8) | (66.4, 72.3) |
| B/Massachusetts/02/2012 | 85.5 ^e | 73.8 |
| (Yamagata lineage) | (83.2, 87.7) | (70.9, 76.5) |
| B/Brisbane/60/2008 | 64.9e | 48.5 |
| (Victoria lineage) | (61.8, 67.9) | (45.3, 51.6) |

CI = Confidence Interval.

^a Trial 4: NCT02242643.

^b According-to-protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

^c A 0.5-mL dose containing 15 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

^d A 0.25-mL dose of U.S.-licensed quadrivalent, inactivated influenza vaccine (manufactured by Sanofi Pasteur Inc.) containing 7.5 mcg each of A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/02/2012 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

^e Non-inferior to the comparator vaccine based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (comparator/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper limit of the 2-sided 95% CI on difference of comparator vaccine minus FLULAVAL QUADRIVALENT ≤10%).

f Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-vaccination titer $\ge 1:10$, or an increase in titer from <1:10 to $\ge 1:40$.

Trial 2 was a randomized, double-blind, active-controlled trial conducted in children aged 3 through 17 years. In this trial, subjects received FLULAVAL QUADRIVALENT (n = 878), or one of 2 formulations of a comparator trivalent influenza vaccine (FLUARIX, TIV-1, n = 871 or TIV-2 n = 878), each containing an influenza type B virus that corresponded to one of the 2 B viruses in FLULAVAL QUADRIVALENT (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage) [see Adverse Reactions (6.1)].

Immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained 28 days following one or 2 doses of FLULAVAL QUADRIVALENT or the comparators. The immunogenicity endpoints were GMTs adjusted for baseline, and the percentage of subjects who achieved seroconversion, defined as at least a 4-fold increase in serum HI titer over baseline to ≥1:40, following vaccination, performed on the ATP cohort. FLULAVAL QUADRIVALENT was non-inferior to both TIVs based on adjusted GMTs and seroconversion rates (Table 10). The antibody response to influenza B strains contained in FLULAVAL QUADRIVALENT was higher than the antibody response after vaccination with a TIV containing an influenza B strain from a different lineage. There was no evidence that the addition of the second B strain resulted in immune interference to other strains included in the vaccine (Table 10).

Table 10. Non-inferiority of FLULAVAL QUADRIVALENT Relative to Trivalent Influenza Vaccine (TIV) at 28 Days Post-vaccination in Children Aged 3 through 17 Years^a (According-to-

Protocol Cohort for Immunogenicity)^b

| | FLULAVAL | TIV-1 | TIV-2 |
|----------------------------|--------------------|---------------------------|---------------------------|
| | QUADRIVALENT° | (B Victoria) ^d | (B Yamagata) ^e |
| Geometric Mean Titers | n = 878 | n = 871 | n = 877 - 878 |
| Against | (95% CI) | (95% CI) | (95% CI) |
| A/California/7/2009 (H1N1) | $362.7^{\rm f}$ | 429.1 | 420.2 |
| | (335.3, 392.3) | (396.5, 464.3) | (388.8, 454.0) |
| A/Victoria/210/2009 | 143.7 ^f | 139.6 | 151.0 |
| (H3N2) | (134.2, 153.9) | (130.5, 149.3) | (141.0, 161.6) |
| B/Brisbane/60/2008 | $250.5^{\rm f}$ | 245.4 | 68.1 |
| (Victoria lineage) | (230.8, 272.0) | (226.9, 265.4) | (61.9, 74.9) |
| B/Florida/4/2006 | 512.5 ^f | 197.0 | 579.0 |
| (Yamagata lineage) | (477.6, 549.9) | (180.7, 214.8) | (541.2, 619.3) |
| | n = 876 | n = 870 | n = 876-877 |
| Seroconversiong to: | % (95% CI) | % (95% CI) | % (95% CI) |
| A/California/7/2009 (H1N1) | 84.4 ^f | 86.8 | 85.5 |
| | (81.8, 86.7) | (84.3, 89.0) | (83.0, 87.8) |
| A/Victoria/210/2009 | 70.1 ^f | 67.8 | 69.6 |
| (H3N2) | (66.9, 73.1) | (64.6, 70.9) | (66.5, 72.7) |
| B/Brisbane/60/2008 | 74.5 ^f | 71.5 | 29.9 |
| (Victoria lineage) | (71.5, 77.4) | (68.4, 74.5) | (26.9, 33.1) |
| B/Florida/4/2006 | 75.2 ^f | 41.3 | 73.4 |
| (Yamagata lineage) | (72.2, 78.1) | (38.0, 44.6) | (70.4, 76.3) |

CI = Confidence Interval.

^a Trial 2: NCT01198756.

^b According-to-protocol cohort for immunogenicity included all evaluable subjects for whom assay results were available after vaccination for at least one trial vaccine antigen.

^c Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Florida/04/2006 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage).

^d Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage).

^e Containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage).

f Non-inferior to both TIVs based on adjusted GMTs [upper limit of the 2-sided 95% CI for the GMT ratio (TIV/FLULAVAL QUADRIVALENT) ≤1.5] and seroconversion rates (upper limit of the 2-sided 95% CI on difference of the TIV minus FLULAVAL QUADRIVALENT ≤10%); superior to TIV-1 (B Victoria) with respect to the B strain of Yamagata lineage and to TIV-2 (B Yamagata) with respect to the B strain of Victoria lineage based on adjusted GMTs [lower limit of the 2-sided 95% CI

for the GMT ratio (FLULAVAL QUADRIVALENT/TIV)>1.5] and seroconversion rates (lower limit of the 2-sided 95% CI on difference of FLULAVAL QUADRIVALENT minus the TIV >10%).

g Seroconversion defined as a 4-fold increase in post-vaccination antibody titer from pre-vaccination titer $\ge 1:10$, or an increase in titer from <1:10 to $\ge 1:40$.

15 REFERENCES

- 1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res.* 2004;103:133-138.
- 2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb*. 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLULAVAL QUADRIVALENT is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes (packaged without needles) and in 5-mL multi-dose vials containing 10 doses (0.5-mL each).

NDC 19515-906-41 Syringe in Package of 10: NDC 19515-906-52

NDC 19515-897-01 Multi-Dose Vial (containing 10 doses) in Package of 1: NDC 19515-897-11

Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Store in the original package to protect from light. Once entered, a multi-dose vial should be discarded after 28 days.

17 PATIENT COUNSELING INFORMATION

Provide the following information to the vaccine recipient or guardian:

- Inform of the potential benefits and risks of immunization with FLULAVAL QUADRIVALENT.
- Educate regarding potential side effects, emphasizing that (1) FLULAVAL QUADRIVALENT contains non-infectious killed viruses and cannot cause influenza, and (2) FLULAVAL QUADRIVALENT is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.
- Encourage women exposed to FLULAVAL QUADRIVALENT during pregnancy to enroll in the pregnancy registry [see Use in Specific Populations (8.1)].
- Give the Vaccine Information Statements, which are required by the National Childhood Vaccine
 Injury Act of 1986 prior to each immunization. These materials are available free of charge at the
 Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Instruct that annual revaccination is recommended.

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FVQ: xPI

EXHIBIT 254

LE7430, 7433, 7436

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Fluzone[®] Quadrivalent safely and effectively. See full prescribing information for Fluzone Quadrivalent.

Fluzone Quadrivalent (Influenza Vaccine) Suspension for Intramuscular Injection 2019-2020 Formula Initial US Approval (Fluzone Quadrivalent): 2013

-----INDICATIONS AND USAGE-----

Fluzone Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. (1)

Fluzone Quadrivalent is approved for use in persons 6 months of age and older.

-----DOSAGE AND ADMINISTRATION-----

• For intramuscular use only (2)

| | • () | | |
|---------------------------|---|--|---|
| Age | Vaccination Status | Dose | Schedule |
| 6 months through | Not previously vaccinated with influenza vaccine or unknown vaccination history | Two doses, either 0.25 mL or 0.5 mL ^a | Administer at least 4 weeks apart |
| months | Previously vaccinated with influenza vaccine | One or two doses ^b , either 0.25 mL or 0.5 mL ^a | If two doses, administer at least 4 weeks apart |
| 36 months through 8 | Not previously vaccinated with influenza vaccine or unknown vaccination history | Two 0.5 mL doses | Administer at least 4 weeks apart |
| years | Previously vaccinated with influenza vaccine | One or two 0.5 mL doses ^b | If two doses, administer at least 4 weeks apart |
| 9 years and older | - | One 0.5 mL dose | - |

^aThe schedule can be completed as two 0.25-mL doses ≥4 weeks apart, two 0.5-mL doses ≥ 4 weeks apart, or any combination of 2 doses (either 0.25 mL or 0.5 mL) administered ≥4 weeks apart.

-----DOSAGE FORMS AND STRENGTHS-----

Suspension for injection supplied in 4 presentations: prefilled single-dose syringe (pink plunger rod), 0.25 mL; prefilled single-dose syringe (clear plunger rod), 0.5 mL; single-dose vial, 0.5 mL; multi-dose vial, 5 mL. (3)

------CONTRAINDICATIONS-----

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, including egg protein, or after previous dose of any influenza vaccine. (4)

-----WARNINGS AND PRECAUTIONS---

If Guillain-Barré syndrome (GBS) has occurred within 6 weeks following
previous influenza vaccination, the decision to give Fluzone Quadrivalent
should be based on careful consideration of the potential benefits and
risks. (5.1)

----ADVERSE REACTIONS-----

- In children 6 months through 35 months of age, the most common (≥10%) injection-site reactions were pain (57%) or tenderness (47%-54%), erythema (23%-37%), and swelling (13%-22%); the most common solicited systemic adverse reactions were irritability (47%-54%), abnormal crying (33%-41%), malaise (38%), drowsiness (31%-38%), appetite loss (27%-32%), myalgia (27%), vomiting (10%-15%), and fever (11%-14%). (6.1)
- In children 3 years through 8 years of age, the most common (≥10%) injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). (6.1)
- In adults 18 years and older, the most common (≥10%) injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). (6.1)
- In adults 65 years of age and older, the most common (≥10%) injectionsite reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%), (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur Inc., at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Pregnancy exposure registry available. Call Sanofi Pasteur Inc. at 1-800-822-2463.
- Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA - approved patient labeling.

Revised: XX/2020

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17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

^bTo determine if 1 or 2 doses are required, refer to Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines.

[&]quot;-" Indicates information is not applicable

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Fluzone[®] Quadrivalent is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone Quadrivalent is approved for use in persons 6 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular use only

2.1 Dose and Schedule

The dose and schedule for Fluzone Quadrivalent are presented in Table 1.

Prior to vaccination, always refer to the current Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza vaccines.

Table 1: Dose and Schedule for Fluzone Quadrivalent

| Age | Vaccination Status | Dose | Schedule |
|----------------------------|---|---|---|
| 6 months through 35 months | Not previously vaccinated with influenza vaccine or unknown vaccination history | Two doses, either 0.25 mL or 0.5 mL ^a | Administer at least 4 weeks apart |
| | Previously vaccinated with influenza vaccine | One or two doses ^b , either 0.25 mL or 0.5 mL ^a | If two doses, administer at least 4 weeks apart |
| 36 months through 8 years | Not previously vaccinated with influenza vaccine or unknown vaccination | Two 0.5 mL doses | Administer at least 4 weeks apart |

| | history | | |
|-------------------|--|--------------------------------------|---|
| | Previously vaccinated with influenza vaccine | One or two 0.5 mL doses ^b | If two doses, administer at least 4 weeks apart |
| 9 years and older | - | One 0.5 mL dose | - |

^aThe schedule can be completed as two 0.25-mL doses ≥4 weeks apart, two 0.5-mL doses ≥4 weeks apart, or any combination of 2 doses (either 0.25 mL or 0.5 mL) administered \geq 4 weeks apart

2.2 Administration

Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration, whenever solution and container permit. If any of these defects or conditions exist, Fluzone Quadrivalent should not be administered.

Before administering a dose of vaccine, shake the prefilled syringe or vial. Withdraw one dose of vaccine from the single-dose vial using a sterile needle and syringe. Discard unused portion. Use a separate sterile needle and syringe for each dose withdrawn from the multi-dose vial.

The preferred sites for intramuscular injection are the anterolateral aspect of the thigh in infants 6 months through 11 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in persons 12 months through 35 months of age, or the deltoid muscle in persons \geq 36 months of age. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Do not administer this product intravenously, intradermally, or subcutaneously.

^bTo determine if 1 or 2 doses are required, refer to Advisory Committee on Immunization Practices annual recommendations on prevention and control of influenza with vaccines

[&]quot;-" Indicates information is not applicable

Fluzone Quadrivalent should not be combined through reconstitution or mixed with any other vaccine.

3 DOSAGE FORMS AND STRENGTHS

Fluzone Quadrivalent is a suspension for injection.

Fluzone Quadrivalent is supplied in 4 presentations:

- 1) Prefilled single-dose syringe (pink syringe plunger rod), 0.25 mL, for persons 6 months through 35 months of age.
- 2) Prefilled single-dose syringe (clear syringe plunger rod), 0.5 mL, for persons 6 months of age and older.
- 3) Single-dose vial, 0.5 mL, for persons 6 months of age and older.
- 4) Multi-dose vial, 5 mL, for persons 6 months of age and older.

4 CONTRAINDICATIONS

Do not administer Fluzone Quadrivalent to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine [see *Description* (11)], including egg protein, or to a previous dose of any influenza vaccine.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an elevated risk of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with other influenza vaccines is inconclusive; if an excess risk exists, it is probably slightly more than 1 additional case per 1

million persons vaccinated. (See ref. 1) If GBS has occurred within 6 weeks following previous influenza vaccination, the decision to give Fluzone Quadrivalent should be based on careful consideration of the potential benefits and risks.

5.2 Preventing and Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of Fluzone Quadrivalent.

5.3 Altered Immunocompetence

If Fluzone Quadrivalent is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.4 Limitations of Vaccine Effectiveness

Vaccination with Fluzone Quadrivalent may not protect all recipients.

6 ADVERSE REACTIONS

In children 6 months through 35 months of age receiving a 0.25 mL dose of Fluzone Quadrivalent in Study 1 (NCT01240746, see http://clinicaltrials.gov), the most common (\geq 10%) injection-site reactions were pain (57%)^a or tenderness (54%)^b, erythema (37%), and swelling (22%); the most

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^a Assessed in children 24 months through 35 months of age

b Assessed in children 6 months through 23 months of age

common solicited systemic adverse reactions were irritability $(54\%)^b$, abnormal crying $(41\%)^b$, malaise $(38\%)^a$, drowsiness $(38\%)^b$, appetite loss $(32\%)^b$, myalgia $(27\%)^a$, vomiting $(15\%)^b$, and fever (14%). In children 3 years through 8 years of age, the most common $(\ge 10\%)$ injection-site reactions were pain (67%), erythema (34%), and swelling (25%); the most common solicited systemic adverse reactions were myalgia (39%), malaise (32%), and headache (23%). In adults 18 years and older, the most common $(\ge 10\%)$ injection-site reaction was pain (47%); the most common solicited systemic adverse reactions were myalgia (24%), headache (16%), and malaise (11%). In adults 65 years of age and older, the most common $(\ge 10\%)$ injection-site reaction was pain (33%); the most common solicited systemic adverse reactions were myalgia (18%), headache (13%), and malaise (11%).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trial(s) of a vaccine cannot be directly compared to rates in the clinical trial(s) of another vaccine and may not reflect the rates observed in practice.

Children 6 Months Through 8 Years of Age

Study 1 (NCT01240746, see http://clinicaltrials.gov) was a single-blind, randomized, active-controlled multi-center safety and immunogenicity study conducted in the US. In this study, children 6 months through 35 months of age received one or two 0.25 mL doses of either Fluzone Quadrivalent or one of two formulations of a comparator trivalent influenza vaccine (TIV-1 or TIV-2), and children 3 years through 8 years of age received one or two 0.5 mL doses of either Fluzone Quadrivalent, TIV-1, or TIV-2. Each of the trivalent formulations contained an influenza

type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). For participants who received two doses, the doses were administered approximately 4 weeks apart. The safety analysis set included 1841 children 6 months through 35 months of age and 2506 children 3 years through 8 years of age. Among participants 6 months through 8 years of age in the three vaccine groups combined, 49.3% were female (Fluzone Quadrivalent, 49.2%; TIV-1, 49.8%; TIV-2, 49.4%), 58.4% Caucasian (Fluzone Quadrivalent, 58.4%; TIV-1, 58.9%; TIV-2, 57.8%), 20.2% Black (Fluzone Quadrivalent, 20.5%; TIV-1, 19.9%; TIV-2, 19.1%), 14.1% Hispanic (Fluzone Quadrivalent, 14.3%; TIV-1, 13.2%; TIV-2, 14.7%), and 7.3% were of other racial/ethnic groups (Fluzone Quadrivalent, 6.8%; TIV-1, 8.0%; TIV-2, 8.5%). Table 2 and Table 3 summarize solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events for 28 days after each dose and serious adverse events (SAEs) during the 6 months following the last dose.

Table 2: Study 1^a: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Months of Age (Safety Analysis Set)^b

| | Fluzone Quadrivalent ^{c, d} (N ^g =1223) | | | TIV-1 ^{d, e} (B Victoria) (N ^g =310) | | | TIV-2 ^{d, f} (B Yamagata) (N ^g =308) | | |
|--------------------------------|---|--------------------------|-----------------------------|--|-----------------------------|--------------------------|--|-----------------------------|-----------------------------|
| | | | | | | | | | |
| | Any (%) | Grade 2 ^h (%) | Grade 3 ⁱ (%) | Any (%) | Grade 2 ^h (%) | Grade 3 ⁱ (%) | Any (%) | Grade 2 ^h (%) | Grade 3 ⁱ (%) |
| Injection-site | | | | | | | | • | |
| adverse reactions | | | | | | | | | |
| Pain ^j | 57.0 | 10.2 | 1.0 | 52.3 | 11.5 | 0.8 | 50.3 | 5.4 | 2.7 |
| Tenderness ^k | 54.1 | 11.3 | 1.9 | 48.4 | 8.2 | 1.9 | 49.7 | 10.3 | 0.0 |
| Erythema | 37.3 | 1.5 | 0.2 | 32.9 | 1.0 | 0.0 | 33.3 | 1.0 | 0.0 |
| Swelling | 21.6 | 0.8 | 0.2 | 19.7 | 1.0 | 0.0 | 17.3 | 0.0 | 0.0 |
| Systemic | | | | | | | | | |

| | Fluzone Quadrivalent ^{c, d} (N ^g =1223) | | | TIV-1 ^{d, e} (B Victoria) (N ^g =310) | | | TIV-2 ^{d, f} (B Yamagata) (N ^g =308) | | |
|--------------------------------|---|-----------------------------|-----------------------------|--|-----------------------------|--------------------------|--|-----------------------------|--------------------------|
| | | | | | | | | | |
| | Any (%) | Grade 2 ^h (%) | Grade 3 ⁱ (%) | Any (%) | Grade 2 ^h (%) | Grade 3 ⁱ (%) | Any (%) | Grade 2 ^h (%) | Grade 3 ⁱ (%) |
| adverse reactions | | | | | | | | | |
| Fever (≥100.4°F)¹ | 14.3 | 5.5 | 2.1 | 16.0 | 6.6 | 1.7 | 13.0 | 4.1 | 2.0 |
| Malaise ^j | 38.1 | 14.5 | 4.6 | 35.2 | 14.8 | 4.7 | 32.4 | 12.8 | 6.8 |
| Myalgia ^j | 26.7 | 6.6 | 1.9 | 26.6 | 9.4 | 1.6 | 25.0 | 6.8 | 2.7 |
| Headache ^j | 8.9 | 2.5 | 0.6 | 9.4 | 3.9 | 0.0 | 12.2 | 4.7 | 0.0 |
| Irritability ^k | 54.0 | 26.4 | 3.2 | 52.8 | 20.1 | 3.1 | 53.5 | 22.9 | 2.8 |
| Crying abnormal ^k | 41.2 | 12.3 | 3.3 | 36.5 | 8.2 | 1.9 | 29.9 | 10.4 | 2.1 |
| Drowsiness ^k | 37.7 | 8.4 | 1.3 | 32.1 | 3.8 | 0.6 | 31.9 | 5.6 | 0.7 |
| Appetite loss ^k | 32.3 | 9.1 | 1.8 | 33.3 | 5.7 | 1.9 | 25.0 | 8.3 | 0.7 |
| Vomiting ^k | 14.8 | 6.2 | 1.0 | 11.3 | 4.4 | 0.6 | 13.9 | 6.3 | 0.0 |

^aNCT01240746

^bThe safety analysis set includes all persons who received at least one dose of study vaccine

^cFluzone Quadrivalent (0.25 mL) containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^d Participants received 1 or 2 doses according to ACIP recommendations

^e2010-2011 Fluzone TIV (0.25 mL) containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

^fInvestigational TIV (0.25 mL) containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

^gN is the number of participants in the safety analysis set

^hGrade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site tenderness: cries and protests when injection-site is touched; Injection-site erythema, Injection-site swelling: ≥2.5 cm to <5 cm; Fever: >101.3°F to ≤103.1°F (6 months through 23 months); ≥101.2°F to ≤102.0°F (24 months through 35 months); Malaise, Myalgia, and Headache: some interference with activity; Irritability: requiring increased attention; Crying abnormal: 1 to 3 hours; Drowsiness: not interested in surroundings or did not wake up for a feed/meal; Appetite loss: missed 1 or 2 feeds/meals completely; Vomiting: 2 to 5 episodes per 24 hours

¹Grade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site tenderness: cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: >103.1°F (6 months through 23 months); ≥102.1°F (24 months through 35 months); Malaise, Myalgia, and Headache: Significant; prevents daily activity; Irritability: inconsolable; Crying abnormal: >3 hours; Drowsiness: sleeping most of the time or difficult to wake up; Appetite loss: refuses ≥3 feeds/meals or refuses most feeds/meals; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration

^jAssessed in children 24 months through 35 months of age

^kAssessed in children 6 months through 23 months of age

¹Fever measured by any route

Table 3: Study 1^a: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 3 Years Through 8 Years of Age (Safety Analysis Set)^b

| | Fluzone Quadrivalent ^c (N ^f =1669) | | | TIV-1 ^d (B Victoria) (N ^f =424) | | | TIV-2 ^e (B Yamagata) (N ^f =413) | | |
|----------------------------------|--|---------------------------------|--------------------------|---|--------------------------|--------------------------|---|--------------------------|--------------------------|
| | | | | | | | | | |
| | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) |
| Injection-site adverse reactions | | | | | | | | | |
| Pain | 66.6 | 15.8 | 2.1 | 64.6 | 9.5 | 2.0 | 63.8 | 11.6 | 2.8 |
| Erythema | 34.1 | 2.9 | 1.8 | 36.8 | 3.4 | 1.2 | 35.2 | 2.5 | 1.8 |
| Swelling | 24.8 | 2.8 | 1.4 | 25.4 | 1.5 | 1.2 | 25.9 | 2.5 | 1.8 |
| Systemic | | | | | | | | | |
| adverse reactions | | | | | | | | | |
| Fever (≥100.4°F) ⁱ | 7.0 | 2.1 | 2.1 | 7.1 | 2.2 | 1.2 | 7.6 | 2.8 | 0.8 |
| Headache | 23.1 | 6.8 | 2.2 | 21.2 | 5.1 | 2.7 | 24.4 | 7.5 | 2.0 |
| Malaise | 31.9 | 11.2 | 5.5 | 32.8 | 11.4 | 5.6 | 33.4 | 10.8 | 5.0 |
| Myalgia | 38.6 | 12.2 | 3.3 | 34.1 | 9.0 | 2.7 | 38.4 | 11.1 | 2.8 |

^aNCT01240746

Among children 6 months through 8 years of age, unsolicited non-serious adverse events were

reported in 1360 (47.0%) recipients in the Fluzone Quadrivalent group, 352 (48.0%) recipients in

^bThe safety analysis set includes all persons who received at least one dose of study vaccine

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^d2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

^eInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

^fN is the number of participants in the safety analysis set

^gGrade 2 - Injection-site pain: sufficiently discomforting to interfere with normal behavior or activities; Injection-site erythema, Injection-site swelling: \geq 2.5 cm to <5 cm; Fever: \geq 101.2°F to \leq 102.0°F; Headache, Malaise, and Myalgia: some interference with activity

^hGrade 3 - Injection-site pain: incapacitating, unable to perform usual activities; Injection-site erythema, Injection-site swelling: ≥5 cm; Fever: ≥102.1°F; Headache, Malaise, and Myalgia: Significant; prevents daily activity ⁱFever measured by any route

the TIV-1 group, and 346 (48.0%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were cough, vomiting, and pyrexia. During the 28 days following vaccination, a total of 16 (0.6%) recipients in the Fluzone Quadrivalent group, 4 (0.5%) recipients in the TIV-1 group, and 4 (0.6%) recipients in the TIV-2 group, experienced at least one SAE. Throughout the study period, a total of 41 (1.4%) recipients in the Fluzone Quadrivalent group, 7 (1.0%) recipients in the TIV-1 group, and 14 (1.9%) recipients in the TIV-2 group, experienced at least one SAE. Three SAEs were considered to be possibly related to vaccination: croup in a Fluzone Quadrivalent recipient and 2 episodes of febrile seizure, 1 each in a TIV-1 recipient and a TIV-2 recipient.

Study 2 (NCT02915302 see http://clinicaltrials.gov) was a randomized, observer-blinded, 2-arm, multi-center safety and immunogenicity study conducted in the US. In this study, 1950 children 6 months through 35 months of age were randomly assigned to receive Fluzone Quadrivalent administered in either a volume of 0.25 mL (Group 1) or 0.5 mL (Group 2). For participants recommended to receive two doses of influenza vaccine as per Advisory Committee on Immunization Practices guidance, the same dose was administered 4 weeks after the first. The safety analysis set included 1941 participants who received at least 1 dose of study vaccine. Of these participants, 49.7% were female, 74.3% were Caucasian, 19.2% were Black, 6.5% were of other racial groups, and 22.0% were Hispanic/Latino.

Table 4 summarizes solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards for the 0.25 mL and 0.5 mL volumes of Fluzone Quadrivalent in children 6 months through 35 months of age.

Table 4: Study 2^a: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Children 6 Months Through 35 Month of Age (Safety Analysis Set)^b

| | | Quadrivalent | Fluzone Quadrivalent 0.5 mL ^c (N ^d =992) | | | | | | | |
|----------------------------------|----------------------------|--------------------|--|-----------------|--|--|--|--|--|--|
| | 0.2 | 25 mL ^c | | | | | | | | |
| | (N | ^d =949) | | | | | | | | |
| | Any (%) | Grade 3° (%) | Any (%) | Grade 3° (%) | | | | | | |
| Injection-site adverse reactions | | | | | | | | | | |
| Tenderness | 47.3 | 1.7 | 50.4 | 1.2 | | | | | | |
| Redness | 23.1 | 0.0 | 24.3 | 0.2 | | | | | | |
| Swelling | 12.9 | 0.1 | 14.7 | 0.0 | | | | | | |
| Systemic adverse r | Systemic adverse reactions | | | | | | | | | |
| Irritability | 47.4 | 3.6 | 48.6 | 4.0 | | | | | | |
| Abnormal Crying | 33.3 | 3.1 | 34.1 | 2.6 | | | | | | |
| Drowsiness | 31.9 | 2.1 | 31.3 | 1.6 | | | | | | |
| Loss of Appetite | 27.3 | 1.4 | 28.3 | 2.2 | | | | | | |
| Fever (≥100.4°F) ^f | 11.3 | 0.6 | 12.2 | 1.2 | | | | | | |
| Vomiting | 10.0 | 0.4 | 10.2 | 0.5 | | | | | | |

^aNCT02915302

^bThe safety analysis set includes all persons who received at least one dose of study vaccine

^cParticipants received 1 or 2 doses according to ACIP recommendations

^dN is the number of participants in the safety analysis set

[°]Grade 3 - Injection-site tenderness: Cries when injected limb is moved, or the movement of the injected limb is reduced; Injection-site redness, Injection-site swelling: ≥50 mm; Irritability: inconsolable; Abnormal Crying: >3 hours; Drowsiness: sleeping most of the time or difficult to wake up; Loss of Appetite: refuses ≥3 feeds/meals or refuses most feeds/meals; Fever: >103.1°F; Vomiting: ≥6 episodes per 24 hours or requiring parenteral hydration ^fFever measured by any route

The difference in fever rate (Group 2 minus Group 1) was 0.84% (95% CI: -2.13%; 3.80%), meeting the prespecified non-inferiority criterion (upper limit of the 2-sided 95% CI of the difference in fever rates <5%). Participants were monitored for unsolicited adverse events and SAEs during the 28 days following vaccination. Unsolicited non-serious adverse events were reported in 417 (44%) participants in Group 1 and 394 (40%) participants in Group 2. The most commonly reported unsolicited non-serious adverse events in both groups were cough and rhinorrhea. Ten SAEs were reported during the 28-day follow-up period: 5 (0.5%) in Group 1 and 5 (0.5%) in Group 2.

Adults

In Study 3 (NCT00988143, see http://clinicaltrials.gov), a multi-centered randomized, open-label trial conducted in the US, adults 18 years of age and older received one dose of either Fluzone Quadrivalent or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 570 recipients, half aged 18-60 years and half aged 61 years or older. Among participants in the three vaccine groups combined, 67.2% were female (Fluzone Quadrivalent, 68.4%; TIV-1, 67.9%; TIV-2, 65.3%), 88.4% Caucasian (Fluzone Quadrivalent, 91.1%; TIV-1, 86.8%; TIV-2, 87.4%), 9.6% Black (Fluzone Quadrivalent, 6.8%; TIV-1, 12.1%; TIV-2, 10.0%), 0.4% Hispanic (Fluzone Quadrivalent, 0.0%; TIV-1, 0.5%; TIV-2, 0.5%), and 1.7% were of other racial/ethnic groups (Fluzone Quadrivalent, 2.1%; TIV-1, 0.5%; TIV-2, 2.2%). Table 5 summarizes solicited injection-site and systemic

adverse reactions reported within 3 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

Table 5: Study 3^a: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 3 Days After Vaccination in Adults 18 Years of Age and Older (Safety Analysis Set)^b

| | Fluzone Quadrivalent ^c (N ^f =190) | | TIV-1 ^d | | | TIV-2 ^e | | | |
|----------------------------------|--|--------------------------|--------------------------|---------------------------------------|--------------------------|--------------------------|---------------------------------------|--------------------------|--------------------------|
| | | | | (B Victoria) (N ^f =190) | | | (B Yamagata) (N ^f =190) | | |
| | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) |
| Injection-site | | | | | | | | | |
| adverse reactions | | | | | | | | | |
| Pain | 47.4 | 6.8 | 0.5 | 52.1 | 7.9 | 0.5 | 43.2 | 6.3 | 0.0 |
| Erythema | 1.1 | 0.0 | 0.0 | 1.6 | 0.5 | 0.0 | 1.6 | 0.5 | 0.0 |
| Swelling | 0.5 | 0.0 | 0.0 | 3.2 | 0.5 | 0.0 | 1.1 | 0.0 | 0.0 |
| Induration | 0.5 | 0.0 | 0.0 | 1.6 | 0.5 | 0.0 | 0.5 | 0.0 | 0.0 |
| Ecchymosis | 0.5 | 0.0 | 0.0 | 0.5 | 0.0 | 0.0 | 0.5 | 0.0 | 0.0 |
| Systemic | | | | | | | | | |
| adverse reactions | | | | | | | | | |
| Myalgia | 23.7 | 5.8 | 0.0 | 25.3 | 5.8 | 0.0 | 16.8 | 5.8 | 0.0 |
| Headache | 15.8 | 3.2 | 0.5 | 18.4 | 6.3 | 0.5 | 18.0 | 4.2 | 0.0 |
| Malaise | 10.5 | 1.6 | 1.1 | 14.7 | 3.2 | 1.1 | 12.1 | 4.7 | 0.5 |
| Shivering | 2.6 | 0.5 | 0.0 | 5.3 | 1.1 | 0.0 | 3.2 | 0.5 | 0.0 |
| Fever (≥100.4°F) ⁱ | 0.0 | 0.0 | 0.0 | 0.5 | 0.5 | 0.0 | 0.5 | 0.5 | 0.0 |

^aNCT00988143

^bThe safety analysis set includes all persons who received study vaccine

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^d2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

 $^{^{\}rm e}$ 2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed

^fN is the number of participants in the safety analysis set

^gGrade 2 - Injection-site pain: Some interference with activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: \geq 5.1 to \leq 10 cm; Fever: \geq 101.2°F to \leq 102.0°F; Myalgia, Headache, Malaise, and Shivering: some interference with activity

^hGrade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema, Injection-site swelling, Injection-site induration, and Injection-site ecchymosis: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, Malaise, and Shivering: Significant; prevents daily activity

ⁱFever measured by any route

Unsolicited non-serious adverse events were reported in 33 (17.4%) recipients in the Fluzone Quadrivalent group, 45 (23.7%) recipients in the TIV-1 group, and 45 (23.7%) recipients in the TIV-2 group. The most commonly reported unsolicited non-serious adverse events were headache, cough, and oropharyngeal pain. In the follow-up period, there were two SAEs, 1 (0.5%) in the Fluzone Quadrivalent group and 1 (0.5%) in the TIV-2 group.

Geriatric Adults

In Study 4 (NCT01218646, see http://clinicaltrials.gov), a multi-center, randomized, double-blind trial conducted in the US, adults 65 years of age and older received one dose of either Fluzone Quadrivalent, or one of two formulations of comparator trivalent influenza vaccine (TIV-1 or TIV-2). Each of the trivalent formulations contained an influenza type B virus that corresponded to one of the two type B viruses in Fluzone Quadrivalent (a type B virus of the Victoria lineage or a type B virus of the Yamagata lineage). The safety analysis set included 675 recipients. Among participants in the three vaccine groups combined, 55.7% were female (Fluzone Quadrivalent, 57.3%; TIV-1, 56.0%; TIV-2, 53.8%), 89.5% Caucasian (Fluzone Quadrivalent, 87.6%; TIV-1, 89.8%; TIV-2, 91.1%), 2.2% Black (Fluzone Quadrivalent, 4.0%; TIV-1, 1.8%; TIV-2, 0.9%), 7.4% Hispanic (Fluzone Quadrivalent, 8.4%; TIV-1, 7.6%; TIV-2, 6.2%) and 0.9% were of other racial/ethnic groups (Fluzone Quadrivalent, 0.0%; TIV-1, 0.9%; TIV-2, 1.8%).

Table 6 summarizes solicited injection-site and systemic adverse reactions reported within 7 days post-vaccination via diary cards. Participants were monitored for unsolicited adverse events and SAEs during the 21 days following vaccination.

Table 6: Study 4^a: Percentage of Solicited Injection-site and Systemic Adverse Reactions Within 7 Days After Vaccination in Adults 65 Years of Age and Older (Safety Analysis Set)^b

| | Fluzone | | | TIV-1 ^d | | | TIV-2 ^e | | |
|----------------------------------|--|--------------------------|--------------------------|---------------------------------------|--------------------------|--------------------------|---------------------------------------|---------------------------------|-----------------------------|
| | Quadrivalent ^c (N ^f =225) | | | (B Victoria) (N ^f =225) | | | (B Yamagata) (N ^f =225) | | |
| | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) | Any (%) | Grade 2 ^g (%) | Grade 3 ^h (%) |
| Injection-site adverse reactions | | | | | | | | | |
| Pain | 32.6 | 1.3 | 0.9 | 28.6 | 2.7 | 0.0 | 23.1 | 0.9 | 0.0 |
| Erythema | 2.7 | 0.9 | 0.0 | 1.3 | 0.0 | 0.0 | 1.3 | 0.4 | 0.0 |
| Swelling | 1.8 | 0.4 | 0.0 | 1.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Systemic | | | | | | | | | |
| adverse reactions | | | | | | | | | |
| Myalgia | 18.3 | 4.0 | 0.4 | 18.3 | 4.0 | 0.0 | 14.2 | 2.7 | 0.4 |
| Headache | 13.4 | 1.3 | 0.4 | 11.6 | 1.3 | 0.0 | 11.6 | 1.8 | 0.4 |
| Malaise | 10.7 | 4.5 | 0.4 | 6.3 | 0.4 | 0.0 | 11.6 | 2.7 | 0.9 |
| Fever (≥100.4°F) ⁱ | 1.3 | 0.0 | 0.4 | 0.0 | 0.0 | 0.0 | 0.9 | 0.4 | 0.4 |

^aNCT01218646

^bThe safety analysis set includes all persons who received study vaccine

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^d2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

^eInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

^fN is the number of participants in the safety analysis set

^gGrade 2 - Injection-site pain: some interference with activity; Injection-site erythema and Injection-site swelling: \geq 5.1 to \leq 10 cm; Fever: \geq 101.2°F to \leq 102.0°F; Myalgia, Headache, and Malaise: some interference with activity

^hGrade 3 - Injection-site pain: Significant; prevents daily activity; Injection-site erythema and Injection-site swelling: >10 cm; Fever: ≥102.1°F; Myalgia, Headache, and Malaise: Significant; prevents daily activity

ⁱFever measured by any route

Unsolicited non-serious adverse events were reported in 28 (12.4%) recipients in the Fluzone Quadrivalent group, 22 (9.8%) recipients in the TIV-1 group, and 22 (9.8%) recipients in the TIV-2 group. The most commonly reported adverse events were oropharyngeal pain, rhinorrhea, injection-site induration, and headache. Three SAEs were reported during the follow-up period, 2 (0.9%) in the TIV-1 group and 1 (0.4%) in the TIV-2 group.

6.2 Post-Marketing Experience

The following events have been spontaneously reported during the post-approval use of Fluzone (trivalent) or Fluzone Quadrivalent. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to Fluzone (trivalent) or Fluzone Quadrivalent.

- Blood and Lymphatic System Disorders: Thrombocytopenia, lymphadenopathy
- *Immune System Disorders*: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)
- Eye Disorders: Ocular hyperemia
- Nervous System Disorders: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia

- Vascular Disorders: Vasculitis, vasodilatation/flushing
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, cough, wheezing, throat tightness, oropharyngeal pain, rhinorrhea
- Skin and Subcutaneous Tissue Disorders: Rash, pruritus, and Stevens-Johnson syndrome
- General Disorders and Administration Site Conditions: Asthenia/fatigue, pain in extremities, chest pain
- *Gastrointestinal Disorders*: Vomiting

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes following vaccination with Fluzone Quadrivalent during pregnancy.

Healthcare providers are encouraged to enroll women who receive Fluzone Quadrivalent during pregnancy in Sanofi Pasteur Inc.'s vaccination pregnancy registry by calling 1-800-822-2463.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Available data with Fluzone Quadrivalent use in pregnant women are insufficient to inform vaccine-associated risk of adverse developmental outcomes.

A developmental and reproductive toxicity study was performed in female rabbits given a 0.5 mL/dose of Fluzone Quadrivalent prior to mating and during gestation (a single human dose is 0.5 mL). This study revealed no adverse effects to the fetus or pre-weaning development due to Fluzone Quadrivalent [see Animal Data (8.1)].

<u>Data</u>

Animal Data: In a developmental and reproductive toxicity study female rabbits were administered a 0.5 mL/dose of Fluzone Quadrivalent by intramuscular injection 24 and 10 days before insemination, and on Days 6, 12, and 27 of gestation (a single human dose is 0.5 mL). There were no adverse effects on pre-weaning development or vaccine-related fetal malformations noted in this study.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk

Pregnant women are at increased risk of complications associated with influenza infection compared to non-pregnant women. Pregnant women who contract influenza may be at increased risk for adverse pregnancy outcomes, including preterm labor and delivery.

8.2 Lactation

Risk Summary

It is not known whether Fluzone Quadrivalent is excreted in human milk. Data are not available to assess the effects of Fluzone Quadrivalent on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fluzone Quadrivalent and any potential adverse effects on the breastfed child from Fluzone Quadrivalent or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to the disease prevented by the vaccine.

8.4 Pediatric Use

Safety and effectiveness of Fluzone Quadrivalent in children below the age of 6 months have not been established.

8.5 Geriatric Use

Safety and immunogenicity of Fluzone Quadrivalent were evaluated in adults 65 years of age and older. [See *Clinical Studies* (14.6).] Antibody responses to Fluzone Quadrivalent are lower in persons ≥65 years of age than in younger adults.

11 DESCRIPTION

Fluzone Quadrivalent (Influenza Vaccine) for intramuscular injection is an inactivated influenza vaccine, prepared from influenza viruses propagated in embryonated chicken eggs. The viruscontaining allantoic fluid is harvested and inactivated with formaldehyde. Influenza virus is concentrated and purified in a linear sucrose density gradient solution using a continuous flow centrifuge. The virus is then chemically disrupted using a non-ionic surfactant, octylphenol ethoxylate (Triton® X-100), producing a "split virus". The split virus is further purified and then

suspended in sodium phosphate-buffered isotonic sodium chloride solution. The Fluzone Quadrivalent process uses an additional concentration factor after the ultrafiltration step in order to obtain a higher hemagglutinin (HA) antigen concentration. Antigens from the four strains included in the vaccine are produced separately and then combined to make the quadrivalent formulation.

Fluzone Quadrivalent suspension for injection is clear and slightly opalescent in color.

Antibiotics are not used in the manufacture of Fluzone Quadrivalent.

The Fluzone Quadrivalent prefilled syringe and vial presentations are not made with natural rubber latex.

Fluzone Quadrivalent is standardized according to United States Public Health Service requirements and is formulated to contain HA of each of the following four influenza strains recommended for the 2019-2020 influenza season: A/Brisbane/02/2018 IVR-190 (H1N1), A/Kansas/14/2017 X-327 (H3N2), B/Phuket/3073/2013 (B Yamagata lineage), and B/Maryland/15/2016 BX-69A (a B/Colorado/6/2017-like virus, B Victoria lineage). The amounts of HA and other ingredients per dose of vaccine are listed in Table 7. The single-dose, pre-filled syringe (0.25 mL and 0.5 mL) and the single-dose vial (0.5 mL) are manufactured and formulated without thimerosal or any other preservative. The 5 mL multi-dose vial presentation contains thimerosal, a mercury derivative, added as a preservative. Each 0.5 mL dose from the multi-dose vial contains 25 mcg mercury. Each 0.25 mL dose from the multi-dose vial contains 12.5 mcg mercury.

Table 7: Fluzone Quadrivalent Ingredients

| Ingredient | Quantity (per dose) | | | |
|---|---|--|--|--|
| ingrement | Fluzone Quadrivalent 0.25 mL Dose | Fluzone Quadrivalent 0.5 mL Dose | | |
| Active Substance: Split influenza virus, inactivated strains ^a : | 30 mcg HA total | 60 mcg HA total | | |
| A (H1N1) | 7.5 mcg HA | 15 mcg HA | | |
| A (H3N2) | 7.5 mcg HA | 15 mcg HA | | |
| B/(Victoria lineage) | 7.5 mcg HA | 15 mcg HA | | |
| B/(Yamagata lineage) | 7.5 mcg HA | 15 mcg HA | | |
| Other: | | | | |
| Sodium phosphate-buffered isotonic sodium chloride solution | QS ^b to appropriate volume | QS ^b to appropriate volume | | |
| Formaldehyde | ≤50 mcg | ≤100 mcg | | |
| Octylphenol ethoxylate | ≤125 mcg | ≤250 mcg | | |
| Preservative | | | | |
| Single-dose presentations | - | - | | |
| Multi-dose presentation (thimerosal) | 12.5 mcg mercury | 25 mcg mercury | | |

^aper United States Public Health Service (USPHS) requirement

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. Since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Since 2001, two distinct lineages of influenza B (Victoria and Yamagata lineages) have co-circulated worldwide. Protection from influenza virus infection has not been correlated with a specific level of hemagglutination inhibition (HI) antibody titer post-vaccination. However, in some human

^bQuantity Sufficient

[&]quot;-" Indicates information is not applicable

studies, antibody titers ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects. (See ref. 2) (See ref. 3)

Antibodies against one influenza virus type or subtype confer limited or no protection against another. Furthermore, antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the hemagglutinins of influenza virus strains representing the influenza viruses likely to be circulating in the US during the influenza season.

Annual vaccination with the influenza vaccine is recommended because immunity during the year after vaccination declines and because circulating strains of influenza virus change from year to year.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fluzone Quadrivalent has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals. Vaccination of female rabbits with Fluzone Quadrivalent revealed no evidence of impaired female fertility [see Animal Data (8.1)].

14 CLINICAL STUDIES

The effectiveness of Fluzone Quadrivalent was demonstrated based on clinical endpoint efficacy data for Fluzone (trivalent influenza vaccine) and on an evaluation of serum HI antibody

responses to Fluzone Quadrivalent. Fluzone Quadrivalent, an inactivated influenza vaccine that contains the hemagglutinins of two influenza A subtype viruses and two influenza type B viruses, is manufactured according to the same process as Fluzone.

14.1 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Children 6 through 24 Months of Age

A randomized, double-blind, placebo-controlled study was conducted at a single US center during the 1999-2000 (Year 1) and 2000-2001 (Year 2) influenza seasons. The intent-to-treat analysis set included a total of 786 children 6 through 24 months of age. Participants received two 0.25 mL doses of either Fluzone (N = 525) or a placebo (N = 261). Among all randomized participants in both years, the mean age was 13.8 months; 52.5% were male, 50.8% were Caucasian, 42.0% were Black, and 7.2% were of other racial groups. Cases of influenza were identified through active and passive surveillance for influenza-like illness or acute otitis media and confirmed by culture. Influenza-like illness was defined as fever with signs or symptoms of an upper respiratory infection. Vaccine efficacy against all influenza viral types and subtypes was a secondary endpoint and is presented in Table 8.

Table 8: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Culture-Confirmed Influenza in Children Aged 6 through 24 Months during the 1999-2000 and 2000-2001 Influenza Seasons – Intent-to-Treat Analysis Set^a

| | Fluzoneb | | | | Placebo ^c | | | | Fluzone vs. Placebo | |
|--|----------------|---------------------------|-------------------------|------------|----------------------|-------|-------------------------|-----------------|---------------------------|---|
| Year | n ^d | $\mathbf{N}^{\mathbf{e}}$ | Rate (n/N) ^f | (95% CI) | n ^d | N^e | Rate (n/N) ^f | (95% CI) | Relative Risk (95% CI) | Percent Relative Reduction ^g (95% CI) |
| Year 1 ^h (1999- 2000) | 15 | 273 | 5.5 | (3.1; 8.9) | 22 | 138 | 15.9 | (10.3; 23.1) | 0.34 (0.18; 0.64) | 66 (36; 82) |
| Year 2 ⁱ (2000- 2001) | 9 | 252 | 3.6 | (1.6; 6.7) | 4 | 123 | 3.3 | (0.9; 8.1) | 1.10 (0.34; 3.50) | -10 (-250; 66) |

^aThe intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated

14.2 Efficacy of Fluzone (Trivalent Influenza Vaccine) in Adults

A randomized, double-blind, placebo-controlled study was conducted in a single US center during the 2007-2008 influenza season. Participants received one dose of either Fluzone vaccine (N = 813), an active comparator (N = 814), or placebo (N = 325). The intent-to-treat analysis set included 1138 healthy adults who received Fluzone or placebo. Participants were 18 through 49 years of age (mean age was 23.3 years); 63.3% were female, 83.1% were Caucasian, and 16.9% were of other racial/ethnic groups. Cases of influenza were identified through active and passive surveillance and confirmed by cell culture and/or real-time polymerase chain reaction (PCR).

bFluzone (0.25 mL): 1999-2000 formulation containing A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage) and 2000-2001 formulation containing A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98 (Yamagata lineage)

^cPlacebo: 0.4% NaCl

^dn is the number of participants with culture-confirmed influenza for the given year of study as listed in the first column

^eN is the number of participants randomly assigned to receive Fluzone or placebo for the given year of study as listed in the column headers (intent-to-treat analysis set)

 $^{^{}f}$ Rate (%) = (n/N) * 100

^gRelative reduction in vaccine efficacy was defined as (1-relative risk) x 100

^hIncludes all culture confirmed influenza cases throughout the study duration for Year 1 (12 months of follow-up)

¹Includes all culture-confirmed influenza cases throughout the study duration for Year 2 (6 months of follow-up)

Influenza-like illness was defined as an illness with at least 1 respiratory symptom (cough or nasal congestion) and at least 1 constitutional symptom (fever or feverishness, chills, or body aches).

Vaccine efficacy of Fluzone against all influenza viral types and subtypes is presented in Table 9.

Table 9: Estimated Efficacy of Fluzone (Trivalent Influenza Vaccine) Against Influenza in Adults Aged 18 through 49 Years during the 2007-2008 Influenza Season – Intent-to-Treat Analysis Set^{a,b}

| Laboratory- Confirmed Symptomatic Influenza | Fluzone ^c (N=813) ^c | | | Placebo ^d (N=325) ^e | | | Fluzone vs. Placebo | |
|--|--|-----------------------|------------|--|-----------------------|-------------|---------------------------|---|
| | n ^f | Rate (%) ^g | (95% CI) | n ^f | Rate (%) ^g | (95% CI) | Relative Risk (95% CI) | Percent Relative Reduction ^h (95% CI) |
| Positive culture | 21 | 2.6 | (1.6; 3.9) | 31 | 9.5 | (6.6; 13.3) | 0.27 (0.16; 0.46) | 73 (54; 84) |
| Positive PCR | 28 | 3.4 | (2.3; 4.9) | 35 | 10.8 | (7.6; 14.7) | 0.32 (0.20; 0.52) | 68 (48; 80) |
| | | | | | | | | |
| Positive culture, positive PCR, or both | 28 | 3.4 | (2.3; 4.9) | 35 | 10.8 | (7.6; 14.7) | 0.32 (0.20; 0.52) | 68 (48; 80) |

^aNCT00538512

14.3 Immunogenicity of Fluzone Quadrivalent in Children 6 Months through 8 Years of Age

^bThe intent-to-treat analysis set includes all enrolled participants who were randomly assigned to receive Fluzone or placebo and vaccinated

^cFluzone: 2007-2008 formulation containing A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (Victoria lineage)

^dPlacebo: 0.9% NaCl

^eN is the number of participants randomly assigned to receive Fluzone or placebo

^fn is the number of participants satisfying the criteria listed in the first column

 $^{{}^{}g}$ Rate (%) = (n/N) * 100

^hRelative reduction in vaccine efficacy was defined as (1 - relative risk) x 100

In Study 1 (NCT01240746) [see *Adverse Reactions* (6.1)], 1419 children 6 months through 35 months of age and 2101 children 3 years through 8 years of age were included in the per-protocol immunogenicity analysis. Participants 6 months through 35 months of age received one or two 0.25 mL doses and participants 3 years through 8 years of age received one or two 0.5 mL doses of Fluzone Quadrivalent, TIV-1, or TIV-2. For participants who received two doses, the doses were administered approximately 4 weeks apart. The distribution of demographic characteristics was similar to that of the safety analysis set [see *Adverse Reactions* (6.1)].

HI antibody geometric mean titers (GMTs) and seroconversion rates 28 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 10 and Table 11).

Table 10: Study 1^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age^b (Per-protocol Analysis Set)^c

| Antigen Strain | Fluzone Quadrivalent ^d N°=2339 | Pooled TIV ^f N°=1181 | | GMT Ratio (95% CI) ^g |
|------------------------------------|---|--|--|------------------------------------|
| | GMT | G | GMT | |
| A (H1N1) | 1124 | 1 | 096 | 1.03 (0.93; 1.14) |
| A (H3N2) | 822 | 8 | 0.99 (0.91; 1.08) | |
| | Fluzone Quadrivalent ^d N°=2339 | TIV-1 ^h (B Victoria) N°=582 | TIV-2 ⁱ (B Yamagata) N°=599 | GMT Ratio (95% CI) ^g |
| | GMT | GMT | GMT GMT | |
| B/Brisbane/60/2008 (B Victoria) | 86.1 | 64.3 | $(19.5)^{j}$ | 1.34 (1.20; 1.50) |
| B/Florida/04/2006 (B Yamagata) | 61.5 | $(16.3)^{k}$ | 58.3 | 1.06 (0.94; 1.18) |

^aNCT01240746

^bParticipants 6-35 months old received 1 or 2 doses (0.25 mL) and participants 3-8 years old received 1 or 2 doses (0.5 mL) as per ACIP recommendation

Table 11: Study 1^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 28 Days Post-Vaccination, Persons 6 Months Through 8 Years of Age^b(Per-protocol Analysis Set)^c

| Antigen Strain | Fluzone Quadrivalent ^d N°=2339 | Pooled TIV ^f N ^e =1181 | | Difference of Seroconversion Rates (95% CI) ^h |
|------------------------------------|---|---|--|--|
| | Ser | oconversion ^g (%) | | |
| A (H1N1) | 92.4 | 91 | .4 | 0.9 (-0.9; 3.0) |
| A (H3N2) | 88.0 | 84.2 | | 3.8 (1.4; 6.3) |
| | Fluzone Quadrivalent ^d N°=2339 | TIV-1 ⁱ (B Victoria) N°=582 | TIV-2 ^j (B Yamagata) N°=599 | Difference of Seroconversion Rates (95% CI) ^h |
| | Ser | oconversiong (%) | | 1 |
| B/Brisbane/60/2008 (B Victoria) | 71.8 | 61.1 | (20.0) ^k | 10.7 (6.4; 15.1) |
| B/Florida/04/2006 (B Yamagata) | 66.1 | (17.9) ¹ | 64.0 | 2.0 (-2.2; 6.4) |

^aNCT01240746

^cPer-protocol analysis set included all persons who had no study protocol deviations

^dFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^eN is the number of participants in the per-protocol analysis set

¹Pooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

^gNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66 ^h2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

ⁱInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

^jTIV-2 did not contain B/Brisbane/60/2008

^kTIV-1 did not contain B/Florida/60/2006

^bParticipants 6-35 months old received 1 or 2 doses (0.25 mL) and participants 3-8 years old received 1 or 2 doses (0.5 mL) as per ACIP recommendations

^cPer-protocol analysis set included all persons who had no study protocol deviations

^dFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^eN is the number of participants in the per-protocol analysis set

^fPooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

gSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer \ge 1:40 or a minimum 4-fold increase for participants with pre-vaccination titer \ge 1:10

^hNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >- 10%

ⁱ2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

^jInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

^kTIV-2 did not contain B/Brisbane/60/2008

¹TIV-1 did not contain B/Florida/04/2006

Non-inferiority immunogenicity criteria based on HI antibody GMTs and seroconversion rates were also met when age subgroups (6 months to <36 months and 3 years to <9 years) were examined. In addition, HI antibody GMTs and seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV and the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

14.4 Immunogenicity of the 0.5 mL Dose of Fluzone Quadrivalent in Children 6 Months through 35 Months of Age

In Study 2 (NCT02915302) [see *Adverse Reactions* (6.1)], 1027 children, 6 months through 35 months of age, were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis set [see *Adverse Reactions* (6.1)].

In this study, children 6 months through 35 months of age received one or two doses of either 0.25 mL or 0.5 mL of Fluzone Quadrivalent. Non-inferiority of the 0.5 mL dose(s) relative to the 0.25 mL dose(s) of Fluzone Quadrivalent was demonstrated for all four strains based on prespecified criteria (lower limit of the 2-sided 95% CI of the ratio of GMTs between groups > 0.667; lower limit of the 2-sided 95% CI of the difference in seroconversion rates >-10%). GMT ratios (GMT_{0.5-mL dose} divided by GMT_{0.25-mL dose}) for the A/H1N1, A/H3N2, B Victoria lineage, and B Yamagata lineage strains were 1.42 (95% CI: 1.16; 1.74), 1.48 (95% CI: 1.21; 1.82), 1.33 (95% CI: 1.09; 1.62), and 1.41 (95% CI: 1.17; 1.70), respectively. Seroconversion rate (SCR) differences (SCR_{0.5-mL dose} minus SCR_{0.25-mL dose}) for the A/H1N1, A/H3N2, B Victoria lineage, and B Yamagata lineage strains were 4.6% (95% CI: -0.4%; 9.6%), 5.1% (95% CI: 0.4%; 9.8%), 1.3% (95% CI: -2.9%; 5.6%), and 2.6% (95% CI: -1.4%; 6.5%).

14.5 Immunogenicity of Fluzone Quadrivalent in Adults ≥18 Years of Age

In Study 3 (NCT00988143) [see *Adverse Reactions* (6.1)], 565 adults 18 years of age and older who had received one dose of Fluzone Quadrivalent, TIV-1, or TIV-2 were included in the perprotocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis set [see *Adverse Reactions* (6.1)].

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following each TIV for all four strains, based on pre-specified criteria (see Table 12).

Table 12: Study 3^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 18 Years of Age and Older (Perprotocol Analysis Set)^b

| Antigen Strain | Fluzone Quadrivalent ^c N ^d =190 | Pooled TIV ^e N ^d =375 | | GMT Ratio (95% CI) ^f |
|------------------------------------|---|---|---|------------------------------------|
| | GMT | G | MT | |
| A (H1N1) | 161 | 1 | 51 | 1.06 (0.87; 1.31) |
| A (H3N2) | 304 | 339 | | 0.90 (0.70; 1.15) |
| | Fluzone Quadrivalent ^c N ^d =190 | TIV-1 ^g (B Victoria) N ^d =187 | TIV-2 ^h (B Yamagata) N ^d =188 | GMT Ratio (95% CI) ^f |
| | GMT | GMT | GMT | |
| B/Brisbane/60/2008 (B Victoria) | 101 | 114 | (44.0) ⁱ | 0.89 (0.70; 1.12) |
| B/Florida/04/2006 (B Yamagata) | 155 | (78.1) ^j | 135 | 1.15 (0.93; 1.42) |

^aNCT00988143

14.6 Immunogenicity of Fluzone Quadrivalent in Geriatric Adults ≥65 Years of Age

In Study 4 (NCT01218646) [see *Adverse Reactions* (6.1)], 660 adults 65 years of age and older were included in the per-protocol immunogenicity analysis. The distribution of demographic characteristics was similar to that of the safety analysis set [see *Adverse Reactions* (6.1)].

HI antibody GMTs 21 days following vaccination with Fluzone Quadrivalent were non-inferior to those following TIV for all four strains, based on pre-specified criteria (see Table 13).

^bPer-protocol analysis set included all persons who had no study protocol deviations

^cFluzone Quadrivalent containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^dN is the number of participants in the per-protocol analysis set

^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

^fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >2/3

^g2009-2010 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

^h2008-2009 Fluzone TIV containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/04/2006 (Yamagata lineage), licensed

ⁱTIV-2 did not contain B/Brisbane/60/2008

^jTIV-1 did not contain B/Florida/04/2006

Seroconversion rates 21 days following Fluzone Quadrivalent were non-inferior to those following TIV for H3N2, B/Brisbane, and B/Florida, but not for H1N1 (see Table 14). The HI antibody GMT following Fluzone Quadrivalent was higher than that following TIV-1 for B/Florida but not higher than that following TIV-2 for B/Brisbane, based on pre-specified criteria (the lower limit of the 2-sided 95% CI of the ratio of the GMTs [Fluzone Quadrivalent divided by TIV] >1.5 for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV). Seroconversion rates following Fluzone Quadrivalent were higher than those following TIV for the B strain not contained in each respective TIV, based on prespecified criteria (the lower limit of the two 2-sided 95% CI of the difference of the seroconversion rates [Fluzone Quadrivalent minus TIV] >10% for each B strain in Fluzone Quadrivalent compared with the corresponding B strain not contained in each TIV).

Table 13: Study 4^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by HI Antibody GMTs at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Perprotocol Analysis Set)^b

| Antigen Strain | Fluzone Quadrivalent ^c N ^d =220 | P , N | GMT Ratio (95% CI) ^f | |
|------------------------------------|---|---|---|------------------------------------|
| | GMT | (| GMT | |
| A (H1N1) | 231 | | 270 | 0.85 (0.67; 1.09) |
| A (H3N2) | 501 | | 1.55 (1.25; 1.92) | |
| | Fluzone Quadrivalent ^c N ^d =220 | TIV-1 ^g (B Victoria) N ^d =219 | TIV-2 ^h (B Yamagata) N ^d =221 | GMT Ratio (95% CI) ^f |
| | GMT | GMT | GMT | |
| B/Brisbane/60/2008 (B Victoria) | 73.8 | 57.9 | (42.2) ⁱ | 1.27 (1.05; 1.55) |
| B/Florida/04/2006 (B Yamagata) | 61.1 | (28.5) ^j | 54.8 | 1.11 (0.90; 1.37) |

^aNCT01218646

Quadrivalent divided by pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >0.66

^g2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

Table 14: Study 4^a: Non-inferiority of Fluzone Quadrivalent Relative to TIV for Each Strain by Seroconversion Rates at 21 Days Post-Vaccination, Adults 65 Years of Age and Older (Per-protocol Analysis Set)^b

| Antigen Strain | Fluzone Quadrivalent ^c N ^d =220 | Pool No | Difference of Seroconversion Rates (95% CI) ^f | |
|------------------------------------|---|---|--|--|
| | Sei | roconversion ^g (% | (o) | |
| A (H1N1) | 65.91 | 6 | 9.77 | -3.86 (-11.50; 3.56) |
| A (H3N2) | 69.09 | 5 | 9.77 (1.96; 17.20) | |
| | Fluzone Quadrivalent ^c N ^d =220 | TIV-1 ^h (B Victoria) N ^d =219 | TIV-2 ⁱ (B Yamagata) N ^d =221 | Difference of Seroconversion Rates (95% CI) ^f |
| | Sei | roconversion ^g (% | | |
| B/Brisbane/60/2008 (B Victoria) | 28.64 | 18.72 | (8.60) ^j | 9.91 (1.96; 17.70) |
| B/Florida/04/2006 (B Yamagata) | 33.18 | (9.13) ^k | 31.22 | 1.96 (-6.73; 10.60) |

^aNCT01218646

^bPer-protocol analysis set included all persons who had no study protocol deviations

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^dN is the number of participants in the per-protocol analysis set

^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

^tNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio of GMTs (Fluzone

^hInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

ⁱTIV-2 did not contain B/Brisbane/60/2008

^jTIV-1 did not contain B/Florida/04/2006

^bPer-protocol analysis set included all persons who had no study protocol deviations

^cFluzone Quadrivalent containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage)

^dN is the number of participants in the per-protocol analysis set

^ePooled TIV group includes participants vaccinated with either TIV-1 or TIV-2

^fNon-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates (Fluzone Quadrivalent minus pooled TIV for the A strains, or the TIV containing the corresponding B strain) was >- 10%

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^gSeroconversion: Paired samples with pre-vaccination HI titer <1:10 and post-vaccination titer $\ge 1:40$ or a minimum 4-fold increase for participants with pre-vaccination titer $\ge 1:10$

^h2010-2011 Fluzone TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage), licensed

ⁱInvestigational TIV containing A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage), non-licensed

^jTIV-2 did not contain B/Brisbane/60/2008

^kTIV-1 did not contain B/Florida/04/2006

15 REFERENCES

- Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998;339:1797-802.
- 2 Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. Virus Res 2004;103:133-138.
- 3 Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutinationinhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg Camb 1972;70:767-777.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Single-dose, prefilled syringe (pink plunger rod), without needle, 0.25 mL (NDC 49281-519-00) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-519-25).

Single-dose, prefilled syringe (clear plunger rod), without needle, 0.5 mL (NDC 49281-419-88) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-419-50).

Single-dose vial, 0.5 mL (NDC 49281-419-58) (not made with natural rubber latex). Supplied as package of 10 (NDC 49281-419-10).

Multi-dose vial, 5 mL (NDC 49281-631-78) (not made with natural rubber latex). Supplied as package of 1 (NDC 49281-631-15). A maximum of ten doses can be withdrawn from the multi-dose vial.

16.2 Storage and Handling

Store all Fluzone Quadrivalent presentations refrigerated at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Discard if vaccine has been frozen.

Do not use after the expiration date shown on the label.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information). Inform the vaccine recipient or guardian:

- Fluzone Quadrivalent contains killed viruses and cannot cause influenza.
- Fluzone Quadrivalent stimulates the immune system to protect against influenza, but does not prevent other respiratory infections.
- Annual influenza vaccination is recommended.
- Report adverse reactions to their healthcare provider and/or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967.
- Sanofi Pasteur Inc. is maintaining a prospective pregnancy exposure registry to collect data on pregnancy outcomes and newborn health status following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-822-2463.

Vaccine Information Statements must be provided to vaccine recipients or their guardians, as required by the National Childhood Vaccine Injury Act of 1986 prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

Fluzone is a registered trademark of Sanofi Pasteur Inc.

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater PA 18370 USA

7430, 7433, 7436



Patient Information Sheet Fluzone® Quadrivalent Influenza Vaccine

Please read this information sheet before getting Fluzone Quadrivalent vaccine. This summary is not intended to take the place of talking with your healthcare provider. If you have questions or would like more information, please talk with your healthcare provider.

What is Fluzone Quadrivalent vaccine?

Fluzone Quadrivalent is a vaccine that helps protect against influenza illness (flu).

Fluzone Quadrivalent vaccine is for people who are 6 months of age and older.

Vaccination with Fluzone Quadrivalent vaccine may not protect all people who receive the vaccine.

Who should not get Fluzone Quadrivalent vaccine?

You should not get Fluzone Quadrivalent vaccine if you:

- ever had a severe allergic reaction to eggs or egg products.
- ever had a severe allergic reaction after getting any flu vaccine.
- are younger than 6 months of age.

Tell your healthcare provider if you or your child have or have had:

- Guillain-Barré syndrome (severe muscle weakness) after getting a flu vaccine.
- problems with your immune system as the immune response may be diminished.

How is the Fluzone Quadrivalent vaccine given?

Fluzone Quadrivalent vaccine is a shot given into the muscle of the arm.

For infants, Fluzone Quadrivalent vaccine is a shot given into the muscle of the thigh.

What are the possible side effects of Fluzone Quadrivalent vaccine?

The most common side effects of Fluzone Quadrivalent vaccine are:

- pain, redness, and swelling where you got the shot
- muscle aches
- tiredness
- headache
- fever

These are not all of the possible side effects of Fluzone Quadrivalent vaccine. You can ask your healthcare provider for a list of other side effects that is available to healthcare professionals.

Call your healthcare provider for advice about any side effects that concern you. You may report side effects to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 or http://vaers.hhs.gov. Sanofi Pasteur Inc. is collecting information on pregnancy outcomes and the health of newborns following vaccination with Fluzone Quadrivalent during pregnancy. Women who receive Fluzone Quadrivalent during pregnancy are encouraged to contact Sanofi Pasteur Inc. directly or have their healthcare provider contact Sanofi Pasteur Inc. at 1-800-822-2463.

What are the ingredients in Fluzone Quadrivalent vaccine?

Fluzone Quadrivalent vaccine contains 4 killed flu virus strains.

Inactive ingredients include formaldehyde and octylphenol ethoxylate. The preservative thimerosal is only in the multi-dose vial of Fluzone Quadrivalent vaccine.

Manufactured by:

Sanofi Pasteur Inc.

Swiftwater, PA 18370 USA

